Does Advanced Imaging Help in the Detection of CRC?

Prof. Nadir Arber

The Tel-Aviv Sourasky Medical Center

Tel Aviv, Israel

ESMO-GI, Barcelona 2016


My Financial Disclosures:
Bayer
Takeda
GI View
Micromedic
Bio View
Check-Cap
Bio-Explorer
Nucleix

Different Screening Modalities

- **Blood tests** ***(Septin9, Medial, CD24)***
- **Stool Tests** ***(FOBT, FIT, Cologuard, M2-PK)***
- **Sigmoidoscopy**
- **Colonoscopy**
- **CT-colonography**
- **Capsule endoscopy** ***(Medtronics, Check-Cap)***

In 2016 Any Screening Modality is Better than Nothing

But colonoscopy is still the best option….

2012: NPS long-term F-U

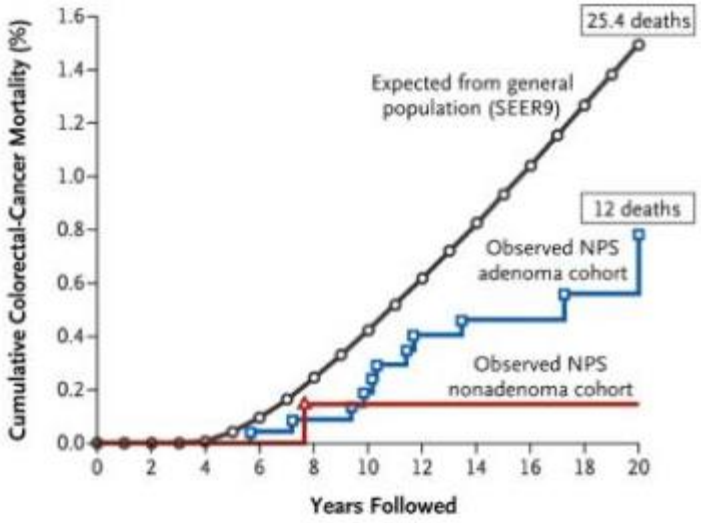
(up to 23 yrs)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 23, 2012 VOL. 366 NO. 8

Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths

Ann G. Zauber, Ph.D., Sidney J. Winawer, M.D., Michael J. O'Brien, M.D., M.P.H., Iris Lansdorp-Vogelaar, Ph.D., Marjolein van Ballegooijen, M.D., Ph.D., Benjamin F. Hankey, Sc.D., Weiji Shi, M.S., John H. Bond, M.D., Melvin Schapiro, M.D., Joel F. Panish, M.D., Edward T. Stewart, M.D., and Jerome D. Waye, M.D.



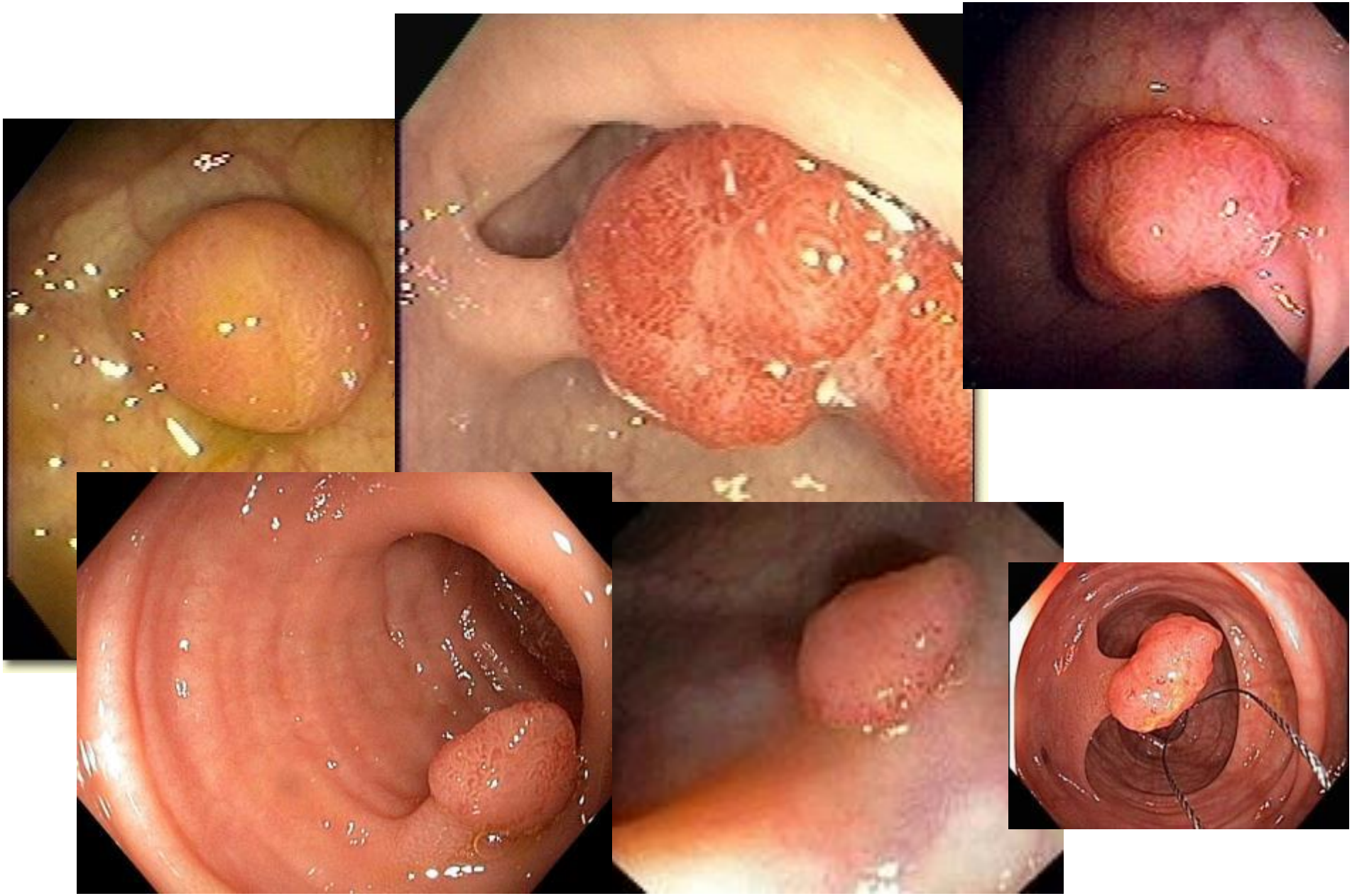
Reduction in CRC mortality with Colonoscopic Polypectomy: 53%

He is perfect……

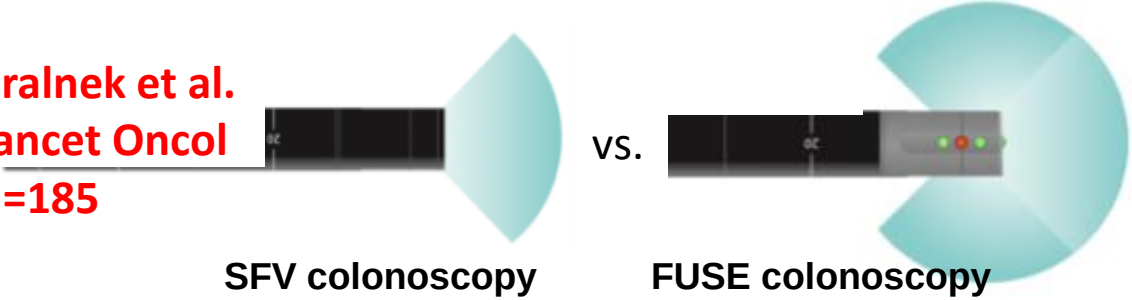
She is perfect……

But colonoscopy is not perfect…

Adenomas are missed…

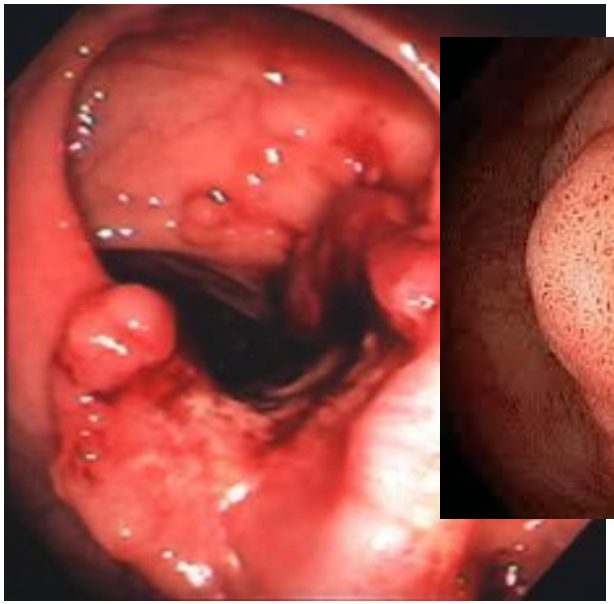


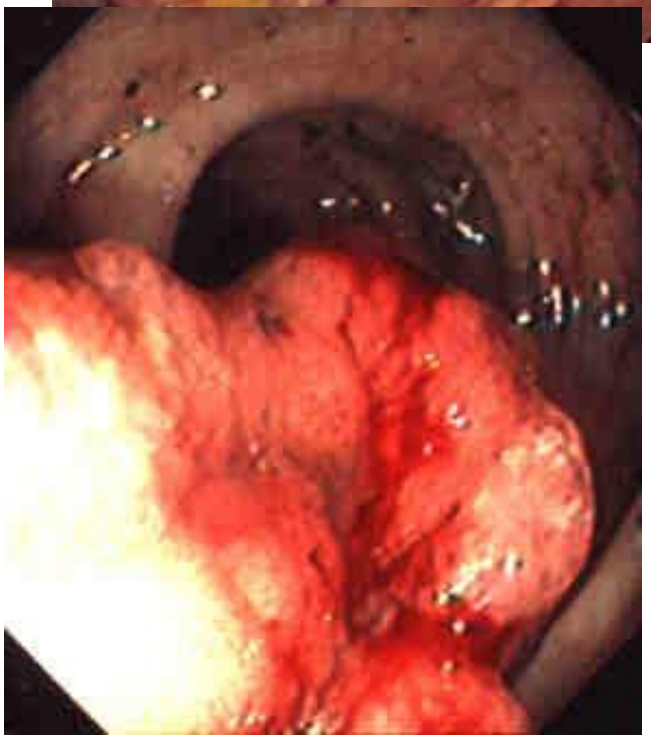
~20% Adenoma Miss Rates in Tandem Colonoscopies

RCT Tandem Studies (per lesion analyses)		Adenoma Miss Rates	Additional Adenomas Detected
Rex et al. Gastro 1997 N=183		SFV 24%	SFV 30.7% (2^{nd} pass)
Van Rijn et al. AJG 2006 N=465 (meta-analysis)		SFV 22.0%	No report
Leufkens et al. GIE 2011 N=349		SFV 31.4% TER 18.4%	SFV 22.6% TER 45.8%
Gralnek et al. Lancet Oncol N=185		**SFV 41% FUSE 7% *P<0.0001***	**SFV 8% FUSE 69% *P<0.0001***

SFV colonoscopy **FUSE colonoscopy**

Thus Interval CRC Can Occur…





Why Do We Miss Adenomas?

- Inadequate colon prep
- Flat/depressed lesions
- Colon anatomy (proximal folds and flexures)
- Suboptimal technique
  - Short withdrawal time
  - Missing cecal intubation

} Low ADR

- Current technology limitations

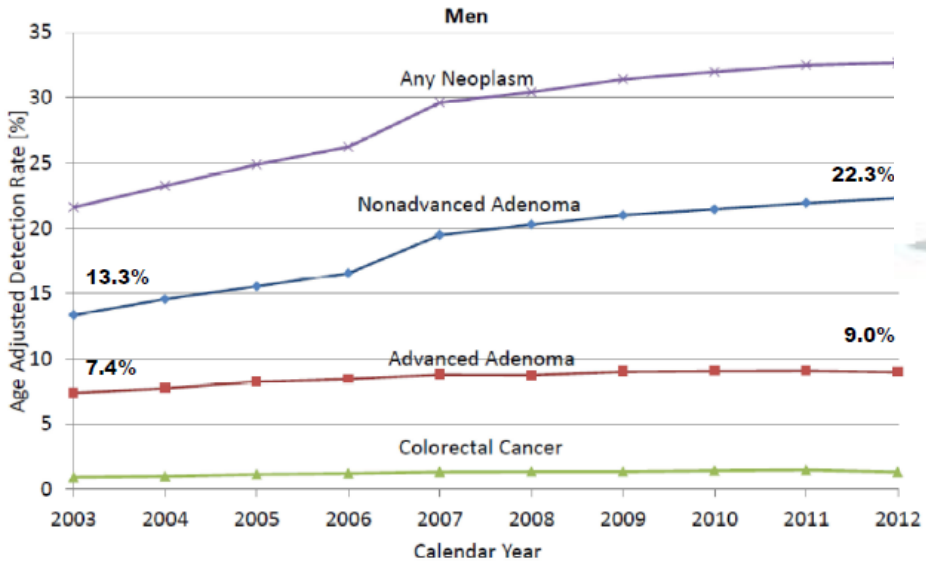
Detection of Small Low-risk Adenoma is the Major Driver of ADR Improvement

Trends in Adenoma Detection Rates During the First 10 Years of the German Screening Colonoscopy Program

Hermann Brenner,[1,2] Lutz Altenhofen,[3] Jens Kretschmann,[3] Thomas Rösch,[4] Christian Pox,[5] Christian Stock,[6] and Michael Hoffmeister[1]

German screening colonoscopy program
4.4 million colonoscopies in a ten year period (2003-2012)

Age-adjusted rates of adenoma detection



Brenner H, Gastroenterology 2015; 149: 356-266

ADR Variation and Risk of Interval Cancer:

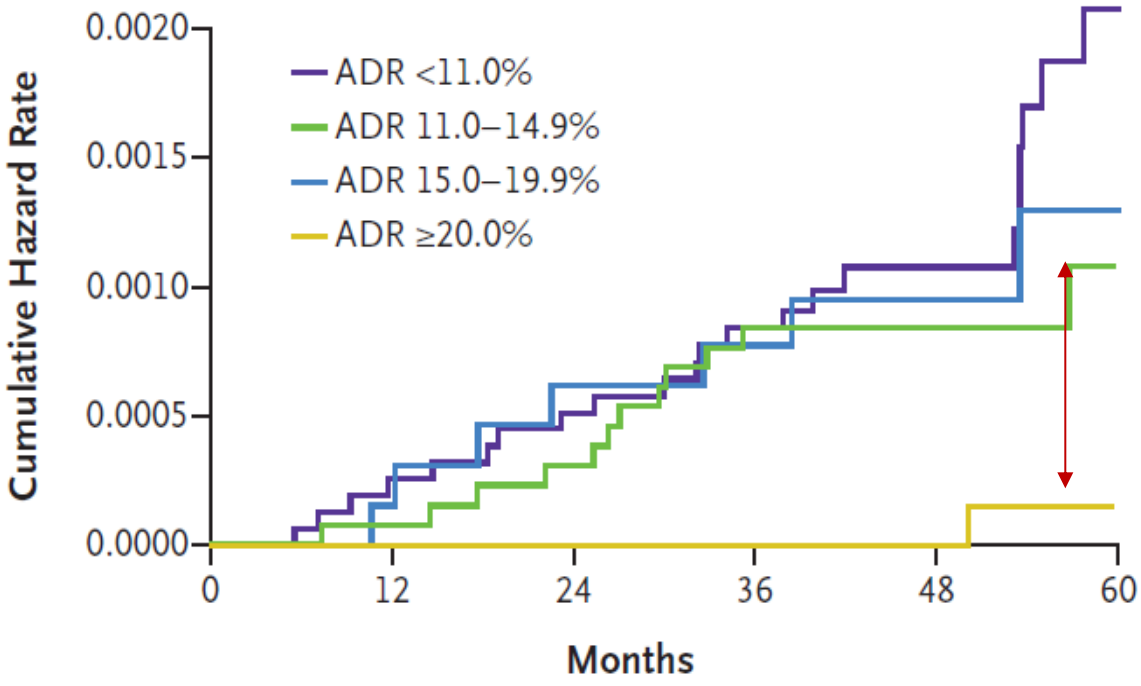
Colonoscopy-based CRC screening

186 endoscopists

46,032 subjects

188,788 persons-years

42 interval cancers

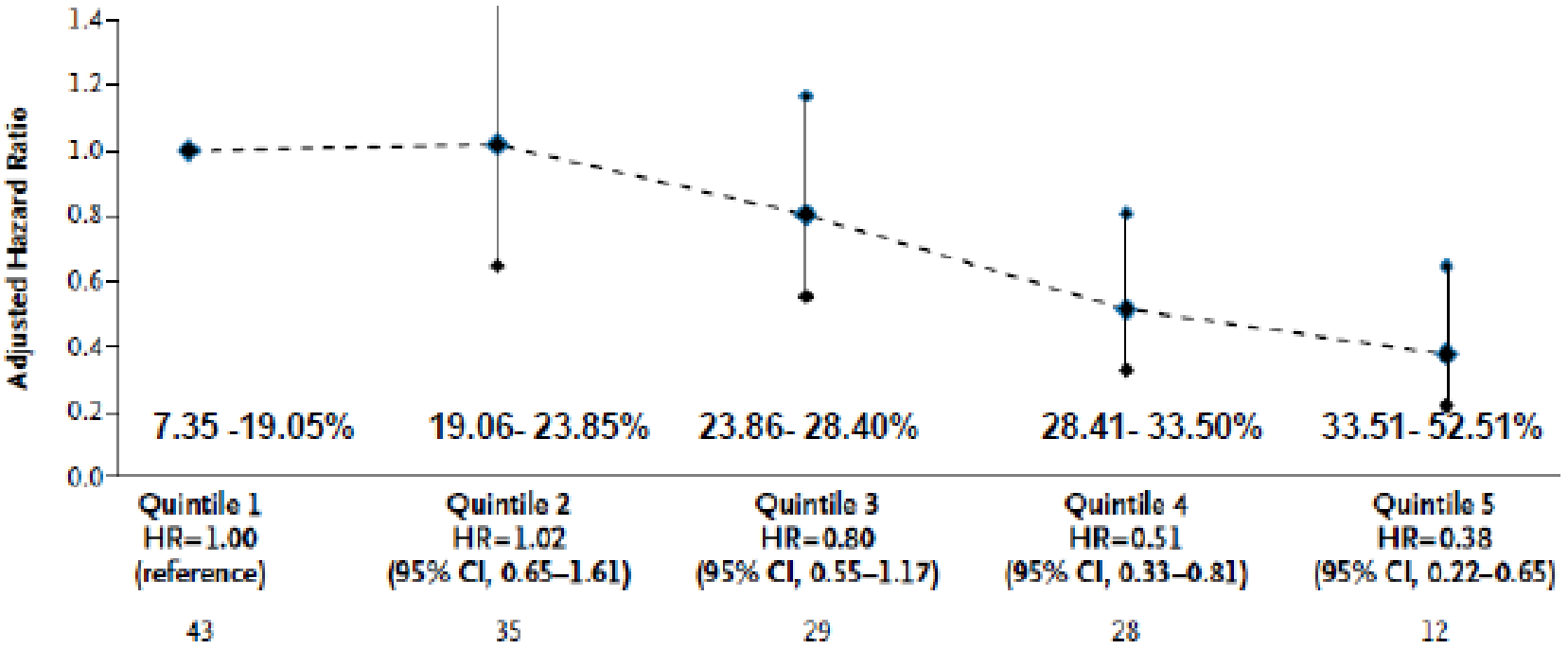


Interval cancers according to ADR;

Endoscopist ADR	HR (95% CI)
≥ 20%	1
15-19.9%	12.50 (1.5-103.4)
11-14.9%	10.75 (1.3-85.0)
< 11%	10.94 (1.3-87.0)

Kaminski MF, N Engl J Med 2010; 362: 1795-803

ADR Variation and Risk of CRC Death:

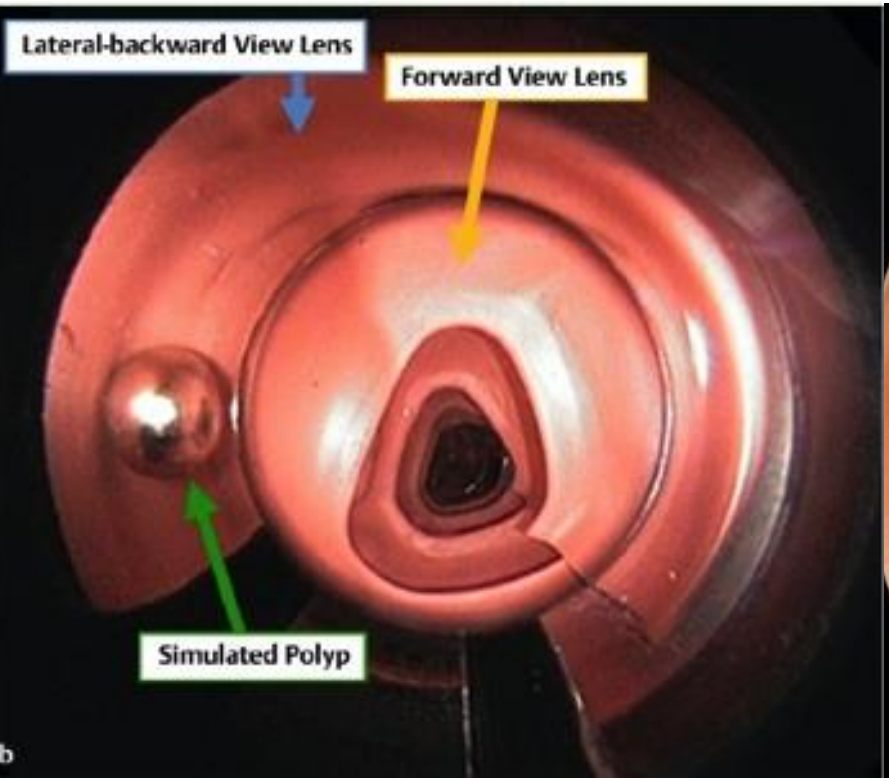


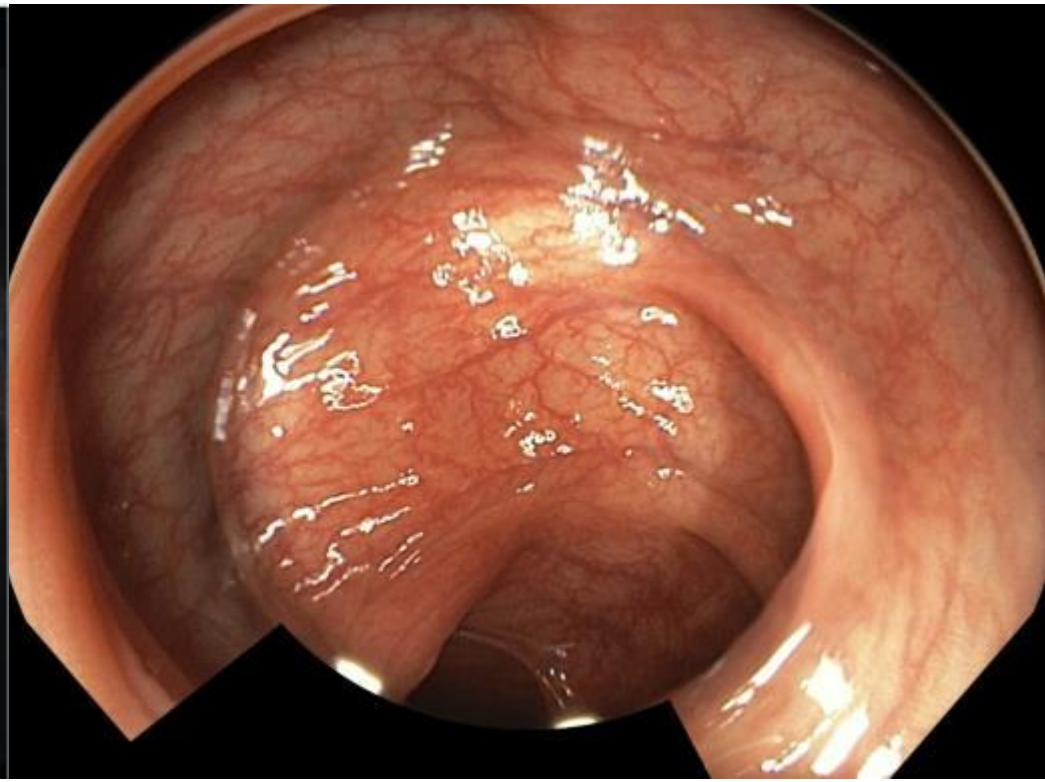
Each 1% ADR increase = 5% decrease in CRC death

Corley DA et al. , N Engl J Med 2014; 370: 1298-803

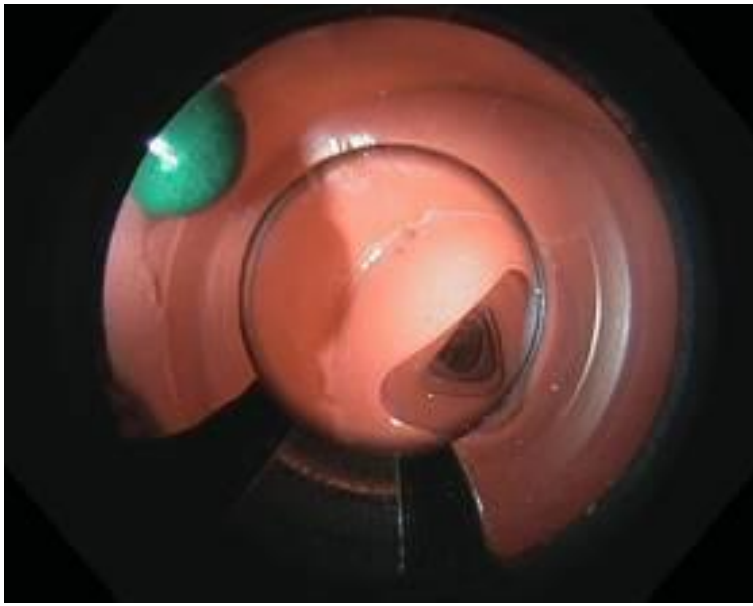
See Better

Extra Wide Angle View Endoscope





Extra-Wide-Angle-View Colonoscope

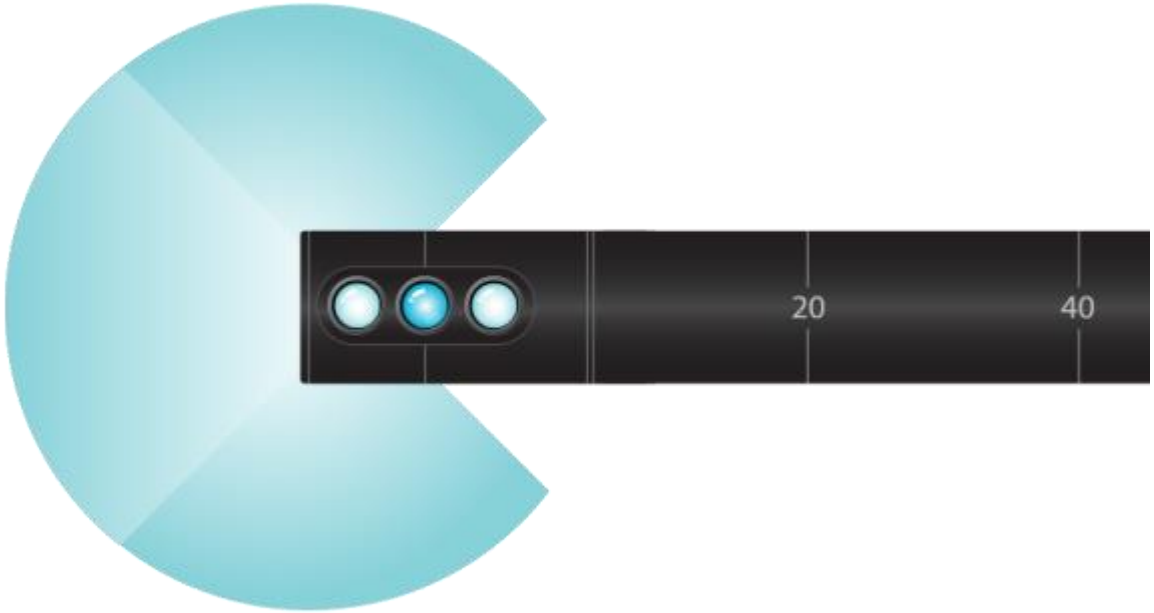


- Extra-wide angle (232°)
- One screen
- Polyp detection
  - All polyps 68% vs 51%, p<0.0001
  - Hidden polyps 62% vs 47%, p<0.0009

Uraoka et al. Gastrointest Endosc 2013

fuse™
Full Spectrum Endoscopy

330°
Field of View



The Fuse Study

Gralnek et al. Lancet Oncol 2014

	SFV followed by Fuse (n=88)	Fuse followed by SFV (n=97)	p-value
Age, years (mean ± SD)	55.9 ± 9.5	55.7 ± 9.7	0.88
Gender, female (%)	46 (52.3%)	55 (56.7%)	0.55
Ottawa Bowel Preparation Score (mean ± SD)	3.4 ± 2.6	3.4 ± 2.8	0.89
Indication for Colonoscopy			
Screening n, (%)	53 (60.2%)	50 (51.5%)	0.24
Surveillance n, (%)	16 (18.2%)	20 (20.6%)	0.68
Diagnostic Evaluation n, (%)	19 (21.6%)	27 (27.9%)	0.33
Additional Adenomas Detected	**69%**	**8%**	**p<0.0001**
Adenoma Miss Rate	**20/49 (40.8%)**	**5/67 (7.5%)**	**p<0.0001**
ADR	**30/88 (34.1%)**	**34/97 (35.1%)**	**0.89**

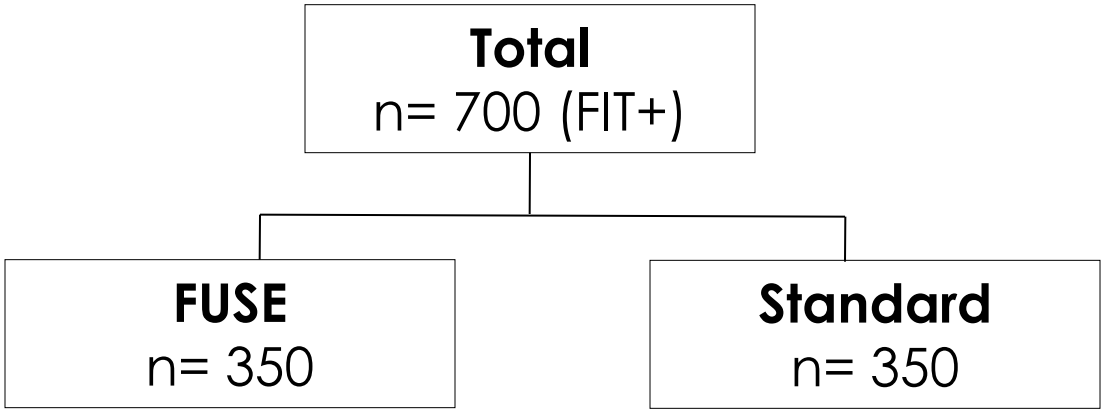
FUSE Study Investigators - Italy

Arnaldo Amato[2], Andrea Anderloni[3], Franco Armelao[5], Arrigo Arrigoni[1], Maurizio Cavina[6], Giovanni DePretis[5], Gianpiero Manes[4], Gianni Miori[5], Alessandra Mondardini[1], Franco Radaelli[2], Alessandro Repici[3], Romano Sassatelli[6], Nereo Segnan[8],

Cesare Hassan[7]

Endoscopy Unit, AOU Città della Salute e della Scienza – Ospedale San Giovanni Antica Sede, Turin[1]; Endoscopy Unit,Ospedale Valduce, Como[2]; Endoscopy Unit, Istituto Clinico Humanitas, Rozzano (Milan)[3]; Endoscopy Unit, Ospedale di Circolo, Rho (Milan)[4]; Endoscopy Unit, Ospedale S Chiara, Trento[5]; Endoscopy Unit, IRCCS S Maria Nuova, Reggio Emilia[6], Endoscopy Unt, Ospedale Nuovo Regina Margherita, Rome[7]; AOU Città della Salute e della Scienza, CPO Piemonte, Turin[8].

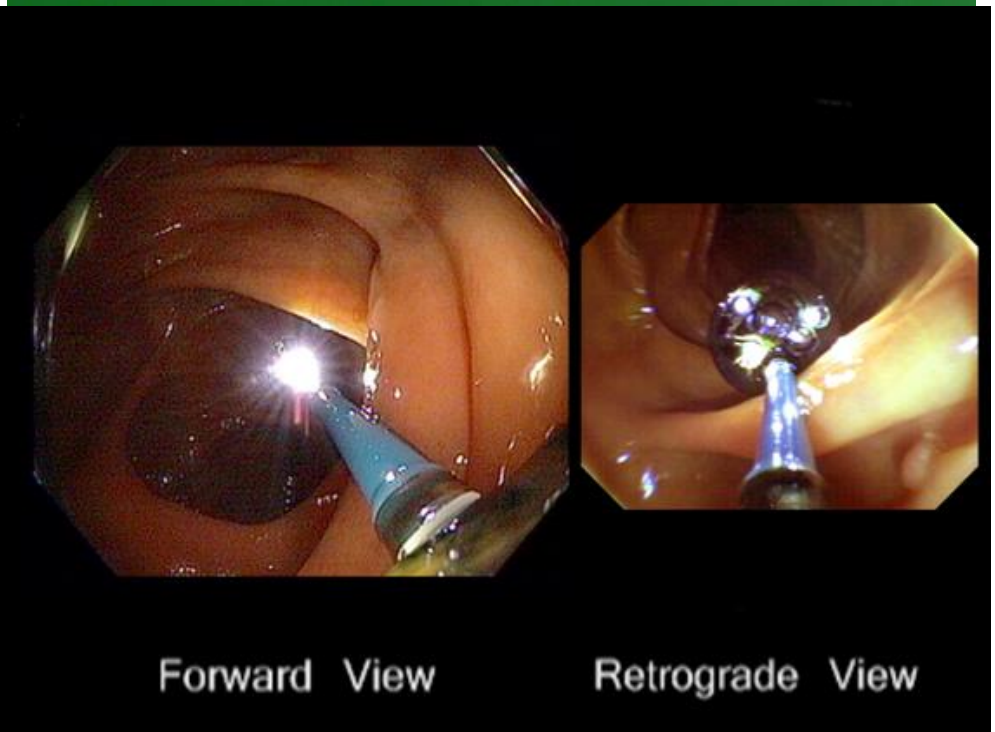
FUSE vs. Standard Endoscopy in Organized Programs - RCT



ADR	42.7%	43.9%
Adv. ADR	19.5%	23.3%


Saneso™
Endoscopy Reinvented™
ARRIVING FALL 2016

Third Eye Retroscope



- *Device that passes through scope channel*
- *Automatically retroflexes 180°*
- *Provides forward and backward view simultaneously on side-by-side monitor*

Courtesy of Prof. Jerry Way

TER: Leufkens et al. GIE 2011

N=349

SFV colonoscopy

VS.

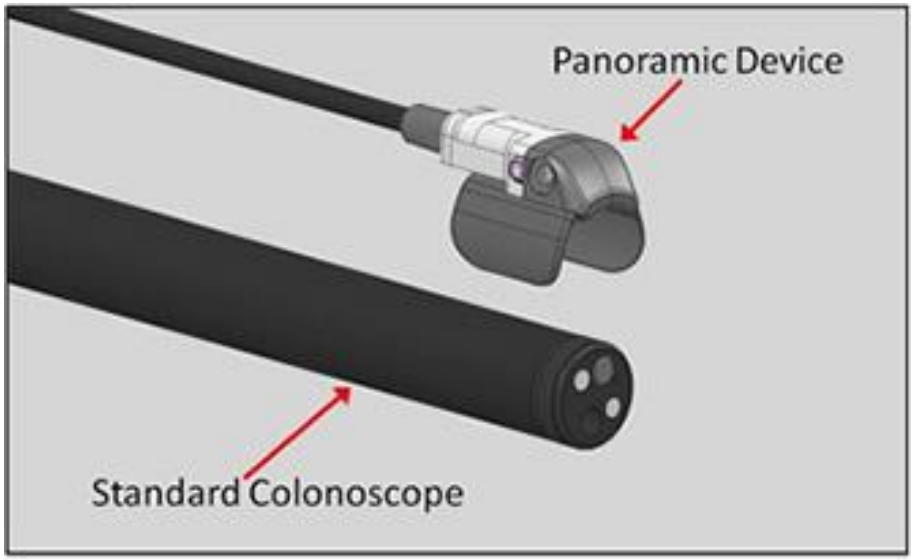
Third-Eye Retroscope

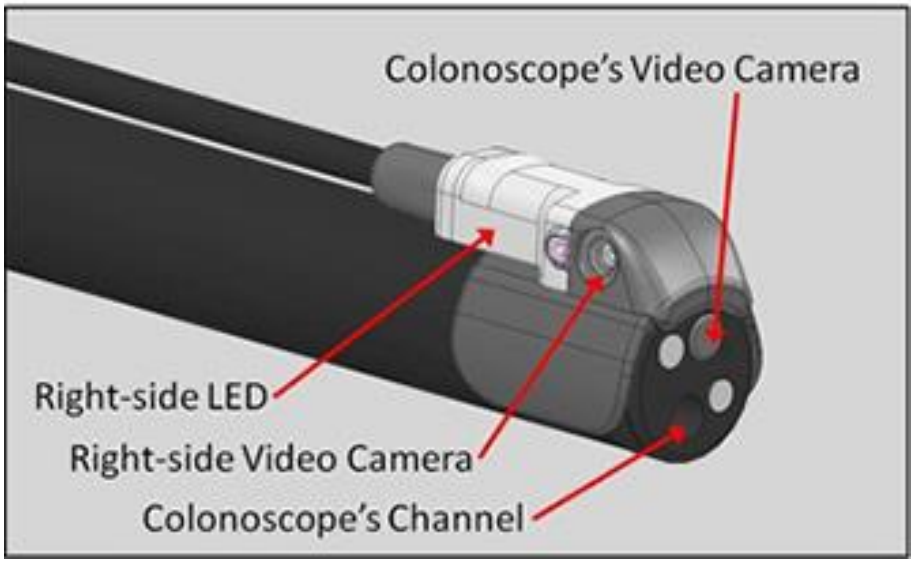
	Adenoma Miss Rates	Additional Adenomas Detected
SFV	31.4%	22.6%
TER	18.4%	45.8%

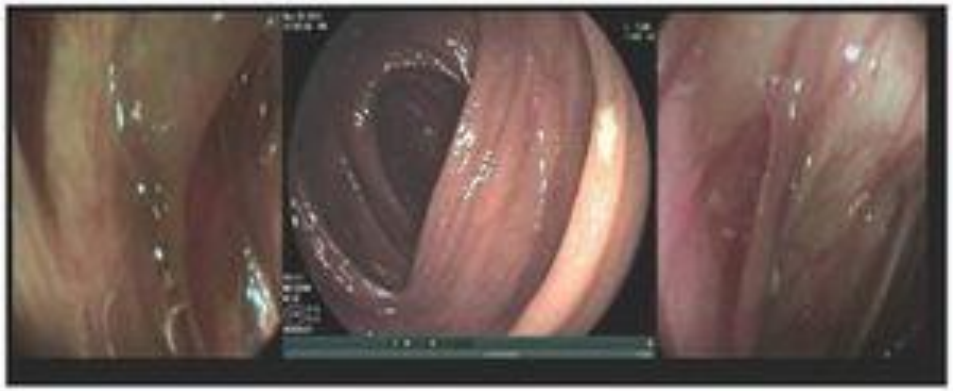
Limitations of Third Eye:

1. *Not user friendly*
2. *Takes up working channel*
3. *Increases procedure time*
4. *Costs*

Third-Eye Panoramic



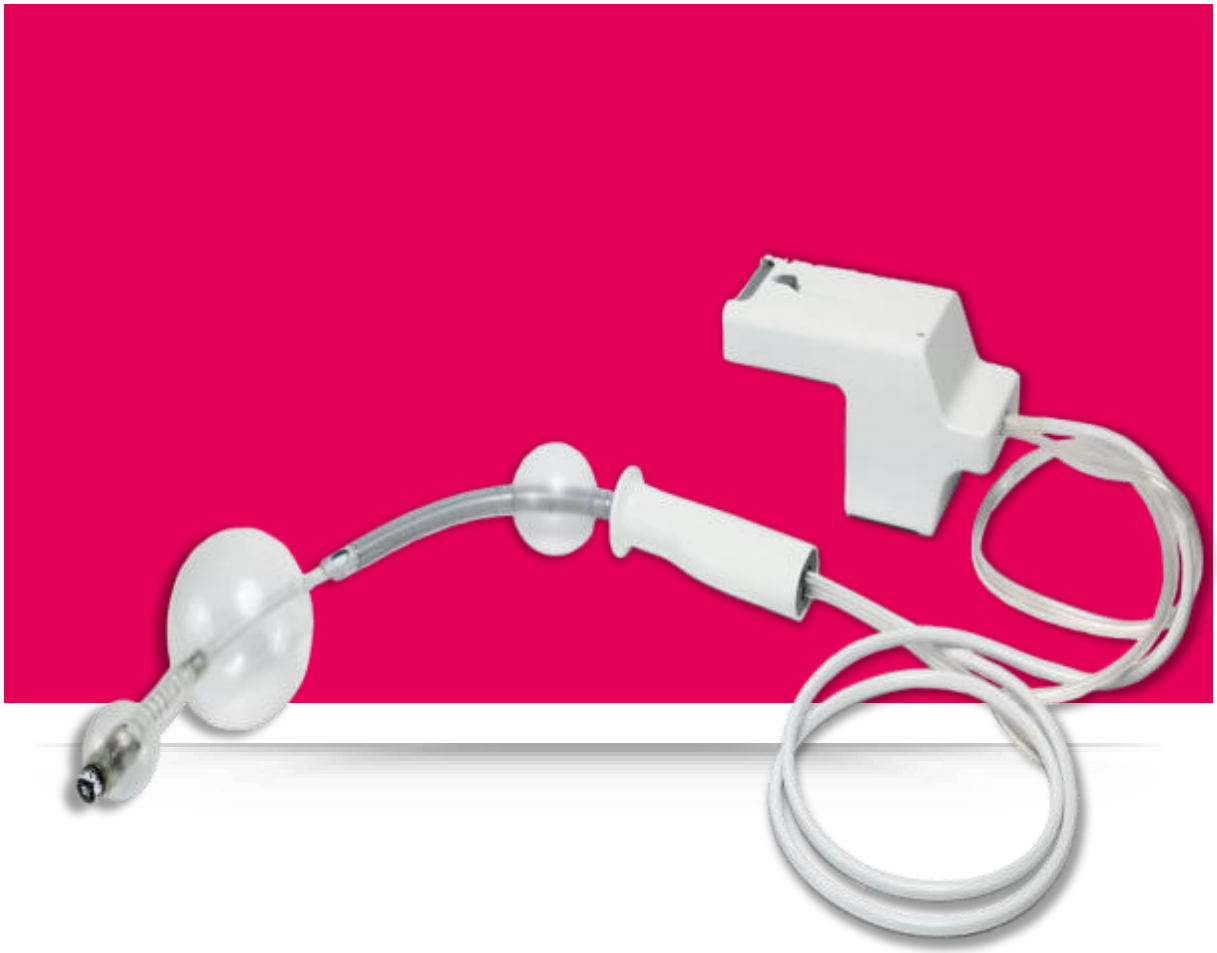




- **Pilot and feasibility**
- **Single use device**
- **CMOS chips, LEDs**
- **N=17**
- **100% cecal intubation**

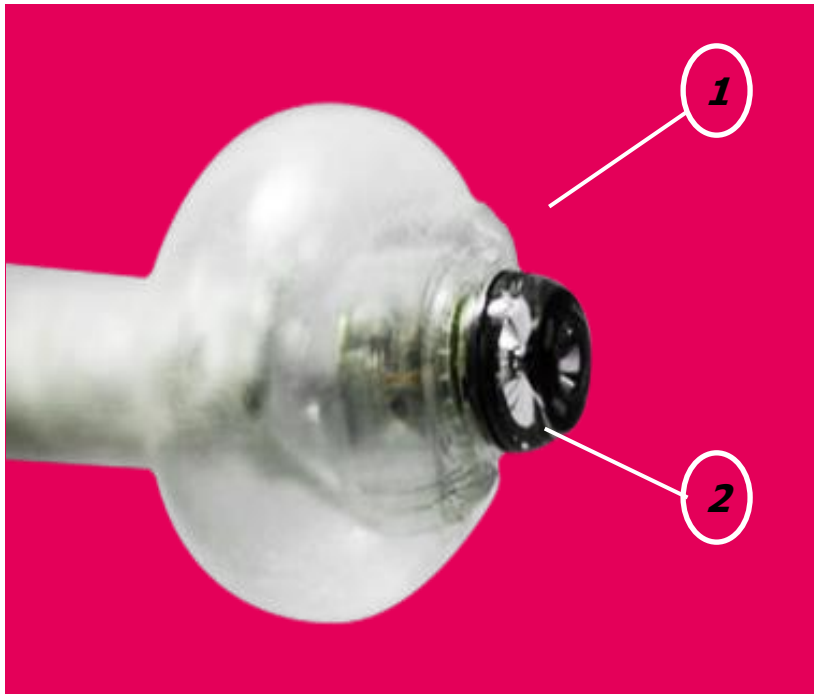
Rubin et al. DDW 2014 abstract

Single Use, Self Propelling, Self Navigating Colonoscope

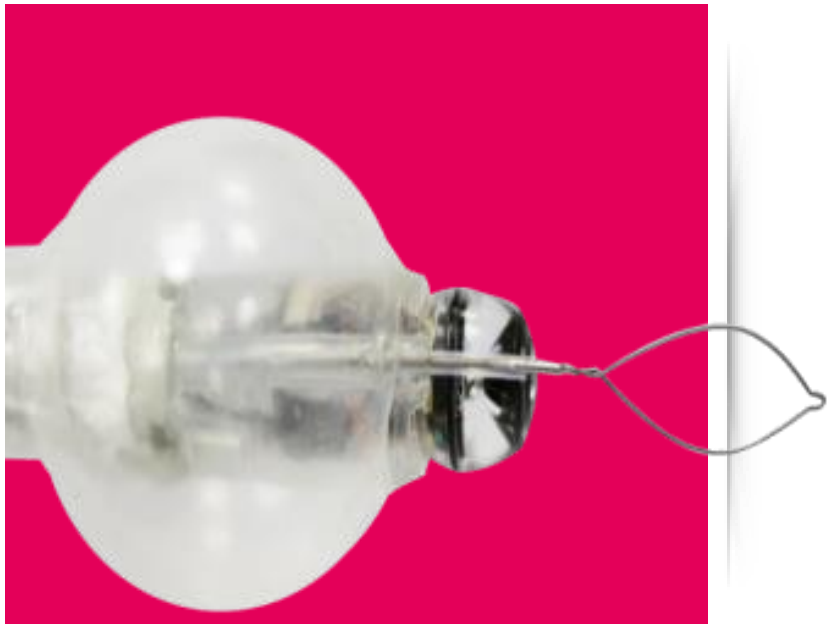


New Scanner with 2 Working Channels

Two Working Channels



2.1 mm channel Supports various 1.8mm tools



Aer-O-Scope™ Key Advantages

- *OMNI-directional 360° vision*
- *Joystick controlled self propelled colonoscope*
- *Scanner induces lower pressure on the colonic wall*
- *Extremely safe system*
- *Disposable*
- *Single operator*
- *The only available FDA approved self propelled colonoscope*

Capsule Endoscopy

Capsule Endoscopy

TABLE 2. Accuracy characteristics for detection of patients with at least one lesion ≥ 6 mm or ≥10 mm

	Colonoscopy	PillCam Colon 2	
Polyp size, mm	Prevalence, no. (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
≥6 mm	45 (41)	84 (74-95)	64 (52-76)
≥10 mm	32 (29)	88 (76-99)	95 (90-100)

CI, Confidence interval.

Pillcam Colonoscopy: What did we learn?

- **ESGE 2012**
  - Average risk patients
  - Incomplete colonoscopy
  - Unwilling to undergo conventional colonoscopy
  - Colonoscopy contraindicated
- **FDA 2014**
  - Incomplete colonoscopy
  - Colonoscopy contraindicated

For	Against
Patient preference	Physician preference Novelty Training Remuneration
Increased capacity	Increased work load
Pan-endoscopy	Histology
Non medical reading	Intervention
Increased access	Cost
Safety?	Time Lag

An expensive Selfi!!!!

Courtesy:
Rami Eliakim

Mechanical Fold Flattening Approach

Cap assisted colonoscopy

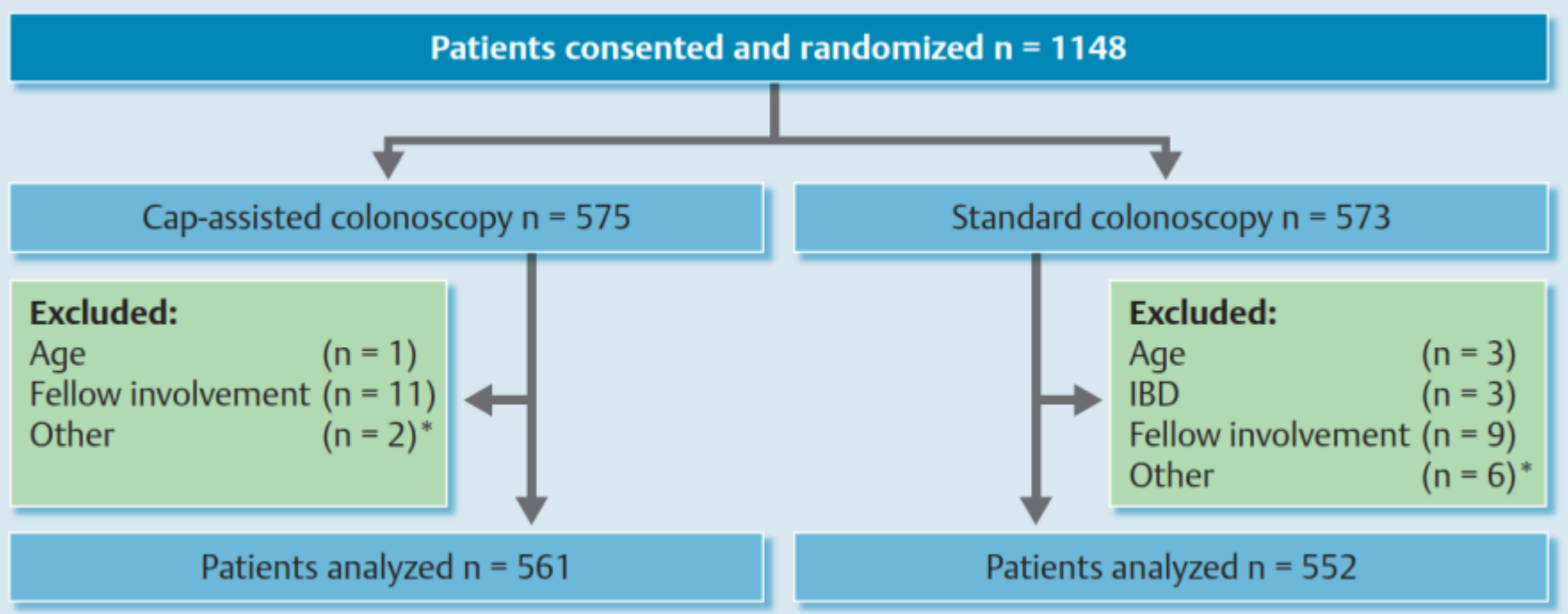
Endocuff/ Endoings
Endoscopic Over tube

G-EYE™ Colonoscope

Cap-assisted colonoscopy and detection of *A*denomatous *P*olyps (CAP) study: a randomized trial

Authors

Heiko Pohl[1,2], Steve P. Bensen[2], Arifa Toor[2], Stuart R. Gordon[2], L. Campbell Levy[2], Brian Berk[2], Peter B. Anderson[2], Joseph C. Anderson[1], Richard I. Rothstein[2], Todd A. MacKenzie[3], Douglas J. Robertson[1]



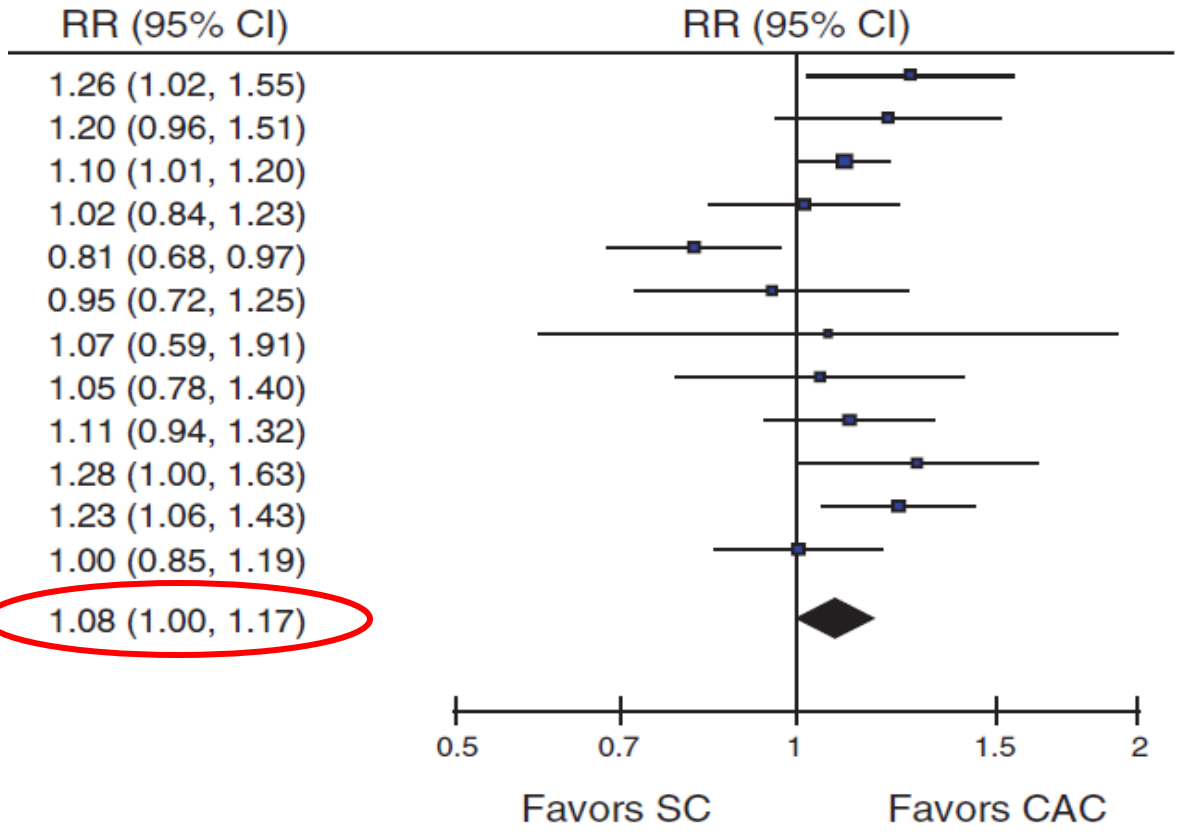
ADR

42%

40%

Cap-Assisted Colonoscopy: A Meta-Analysis with Borderline Efficacy

Endpoint = Polyp Detection

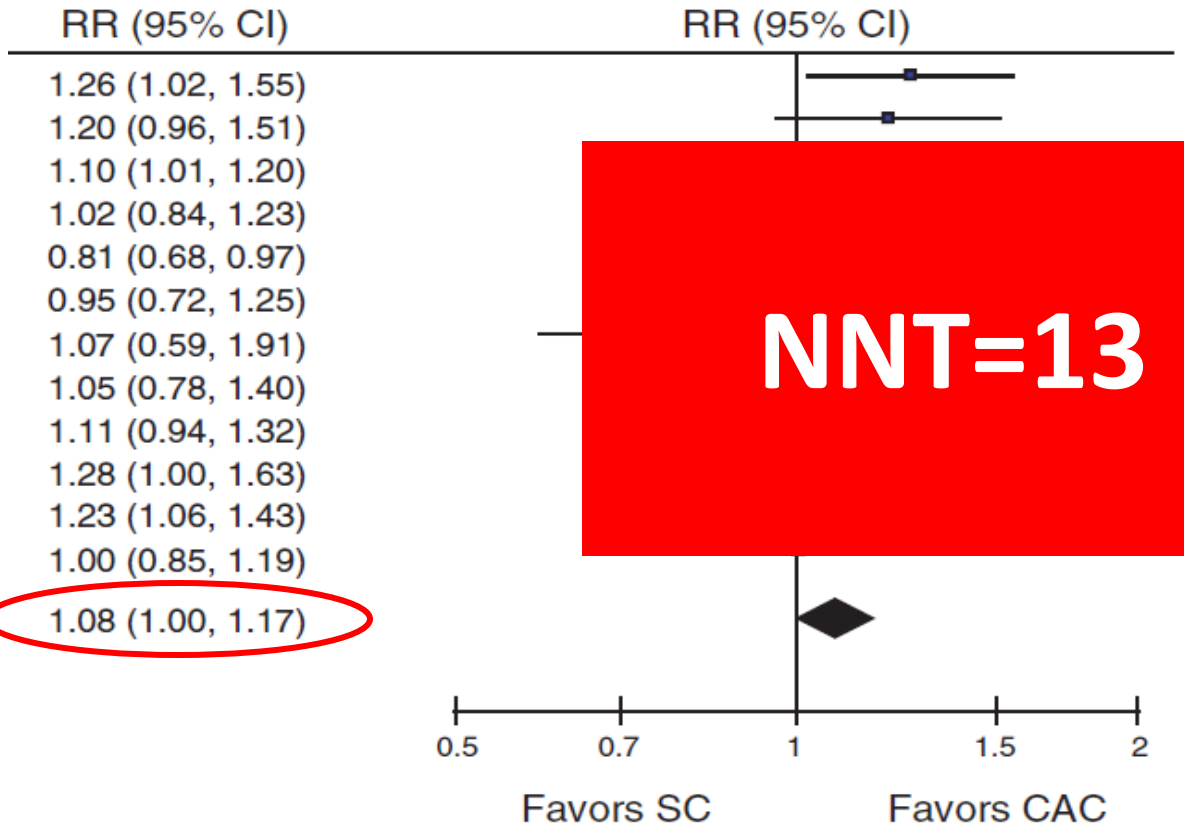


16 RCTs, n= 8,991

Phol et al. Endoscopy 2015, Ng SC et al. Am J Gastroenterol 2012

Cap-Assisted Colonoscopy: A Meta-Analysis with Borderline Efficacy

Endpoint = Polyp Detection



NNT=13

16 RCTs, n= 8,991

Phol et al. Endoscopy 2015, Ng SC et al. Am J Gastroenterol 2012

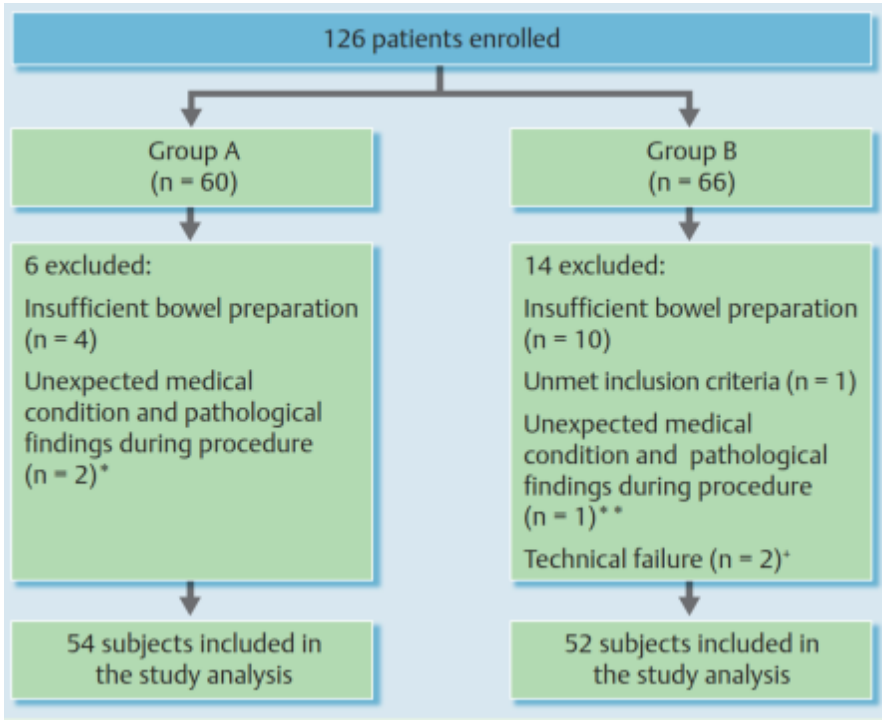
NaviAid™ G-EYE™ Balloon-Colonoscope

- Pentax colonoscope with permanently integrated, reusable balloon
- Balloon inflated by the endoscopist (foot pedal) through the colonoscope internally, no external mounted accessories
- Cecum with balloon deflated
  - ✓ Balloon inflated to engage the colon walls & withdrawn
  - ✓ Mechanical straightening of folds & flexures

Comparison of adenoma detection and miss rates between a novel balloon colonoscope and standard colonoscopy: a randomized tandem study

Authors

Zamir Halpern[1], Seth A. Gross[2], Ian M. Gralnek[3,4], Beni Shpak[5], Mark Pochapin[2], Arthur Hoffman[6], Meir Mizrahi[7], Yosef S. Rochberger[5], Menachem Moshkowitz[5], Erwin Santo[1], Alaa Melhem[1], Roman Grinshpon[1], Jorge Pfefer[1], Ralf Kiesslich[6]



Miss rate adenomas

44.7% ST

7.5% G-EYE

EndoCuff™

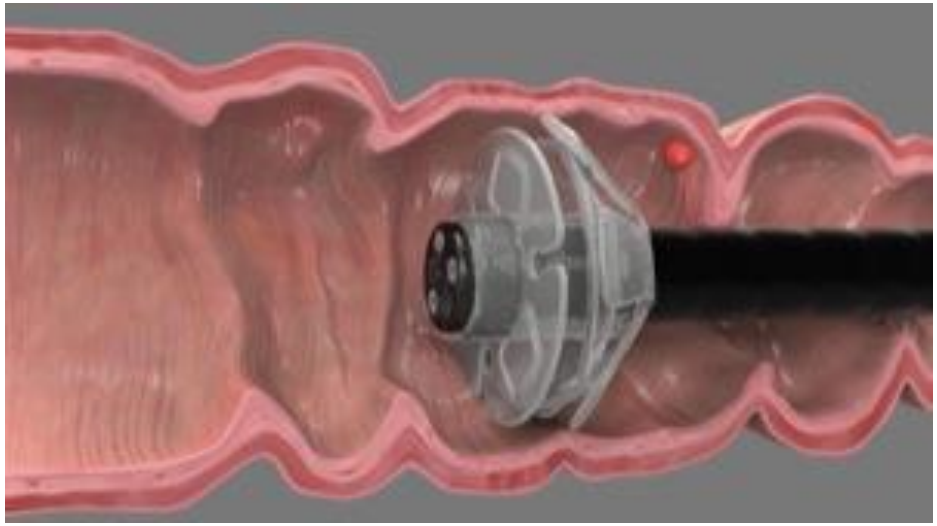
EndoCuff™

- *RCT, 2 centers, n=498*
- *Colonoscopy with and without endocuff,*
- *EC - 63% more polyps detected*
- *PDR = EC 56% vs no EC 42%, p=0.001*
- *EC – significantly more polyps (<1cm) detected in cecum (p=0.001) and sigmoid (p=0.002)*
- *ADR significantly increased by 86% (P=0.002)*
- *No adverse events*

Biecker et al. J Clin Gastroentrol 2015


Comment:

EndoRings™

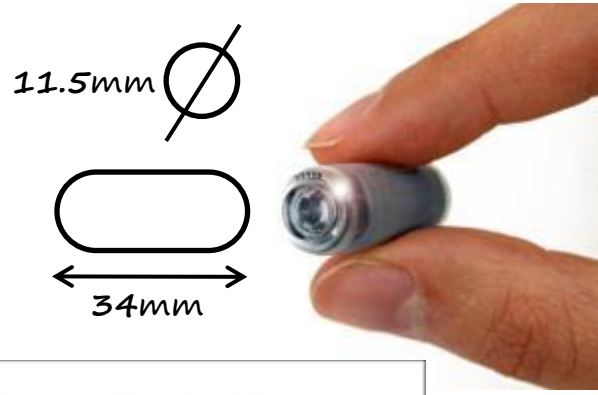


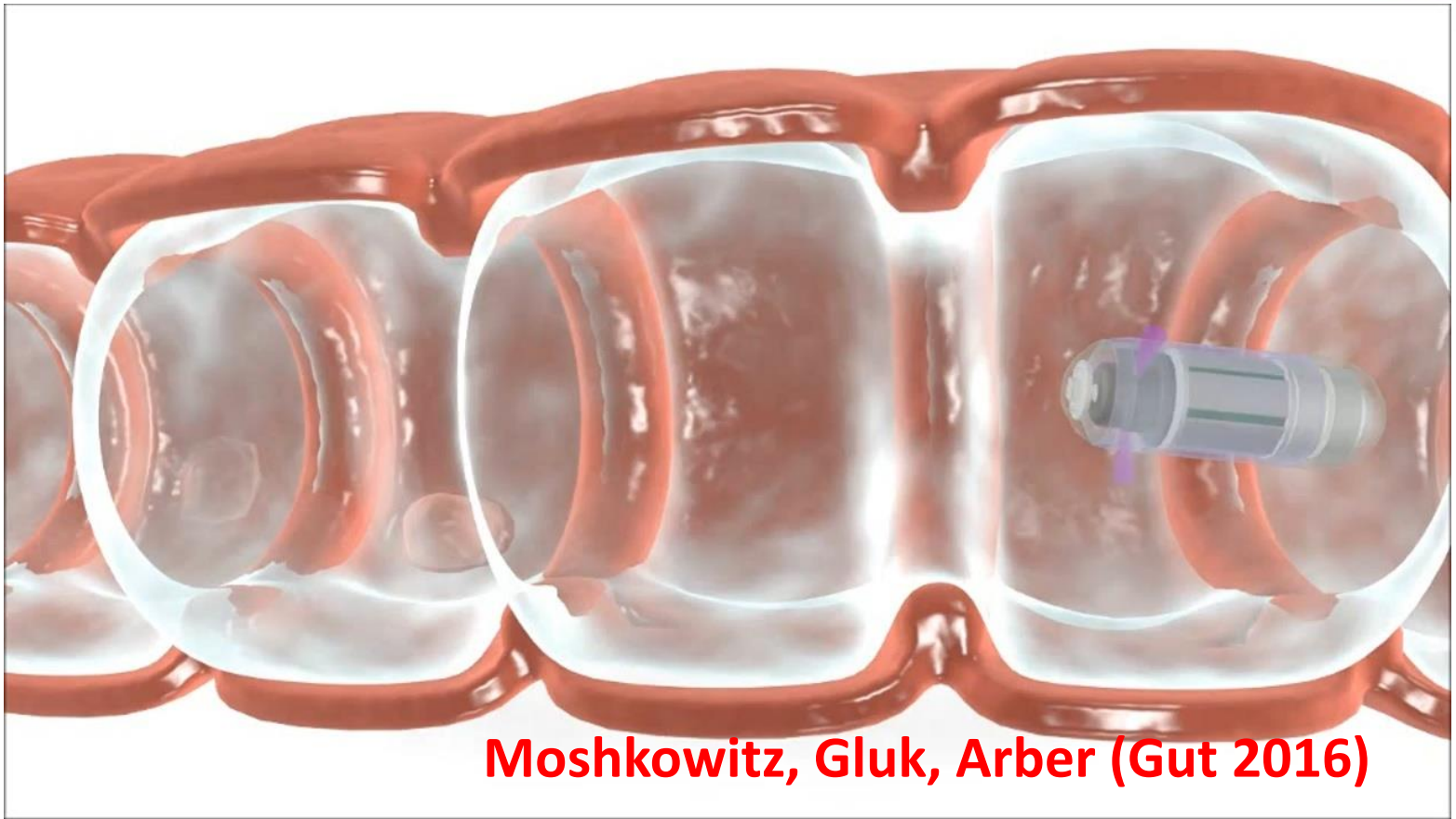
EndoRings – CLEVER Study

- *RCT, N=116* *Dik, Siersema, Gralnek et al. (Endoscopy, 2015)*
- *Tandem colonoscopy design,*
- *Study endpoint = adenoma miss rate*
  - *With endorings = 15%*
  - *Without endorings = 48%, p <0.01*
- *Time to cecum (9.6 min vs. 8.1 min, p=0.17)*
- *Withdrawal times (7.2 vs. 6.8 min, p=0.14)*
- *No adverse events*

Prepless Capsule Colonoscopy: Ultra Low Dose X-ray-Based Imaging Technology (Check-Cap, Israel)

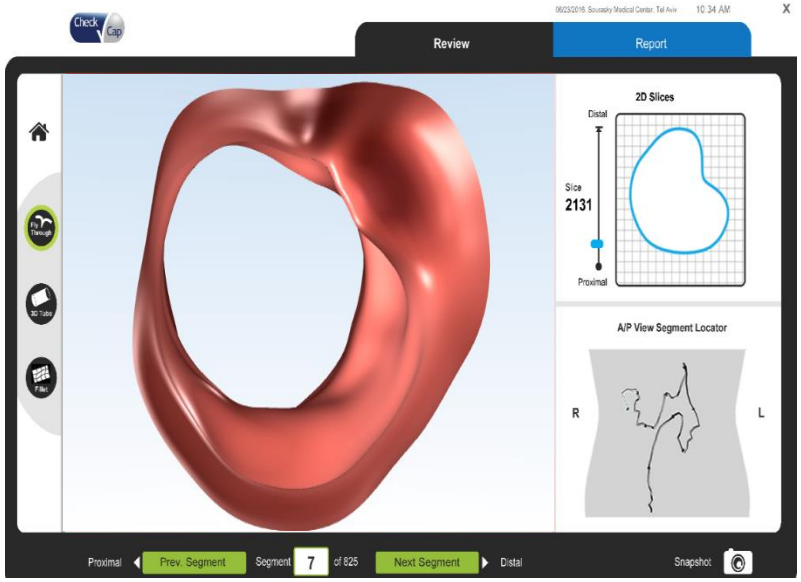
- **Ultra-low dose** (0.03 mSv)
- **Low energy** (56 – 70 Kev)





Moshkowitz, Gluk, Arber (Gut 2016)

#1 Case Study



2D/3D Imaging of a segment with polyp

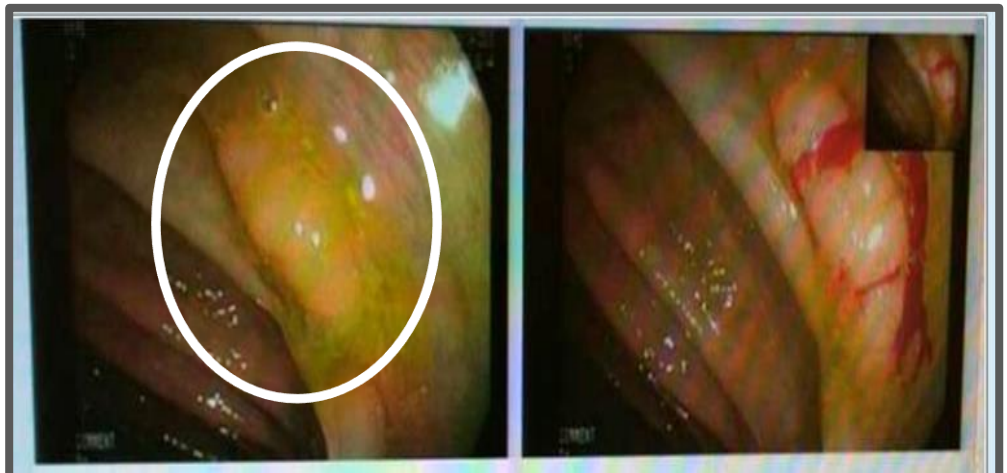
Scanning Capsule finding:

- *A polyp was detected approximately 17 cm above the caecum*

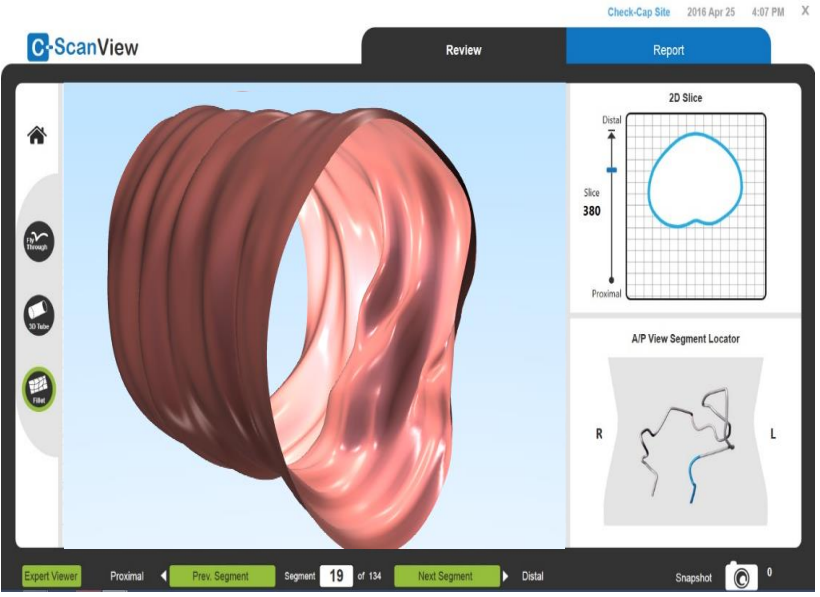
Colonoscopy finding:

- *A 12X4 mm flat sessile polyp on a haustra was detected i18 cm from the bottom part of the caecum*

Colonoscopy images of the polyp



#2 Case Study



2D/3D Imaging of a segment with polyp

Scanning Capsule finding:

- *A pedunculated two heads polyp in the sigmoid colon, measuring 7mm and 15 mm*

Colonoscopy finding:

- *35 cm from the anal verge a 30 mm pedunculated polyp with two hea*

Colonoscopy images of the polyp

Outcome Studies

Hooded colonoscope

3 randomized trials

Current evidence does not indicate any consistent improvement in adenoma detection by hooded colonoscopy

Wide angle colonoscope

10 randomized trials

The only benefit observed was that some operators can withdraw faster without decreasing adenoma detection

Third eye retroscope

A multicenter randomized tandem colonscopy study

No difference between third eye and conventional colonoscopy

Courtesy of Prof. Halpern

Improve Imaging

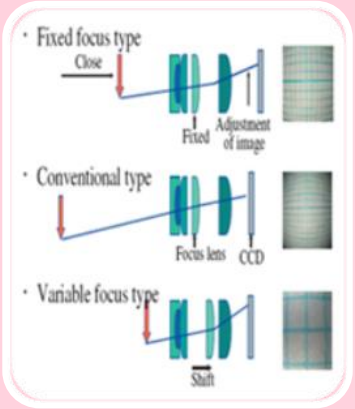
Optic Image

Standard Endoscopy (SD)

0.4 megapixel

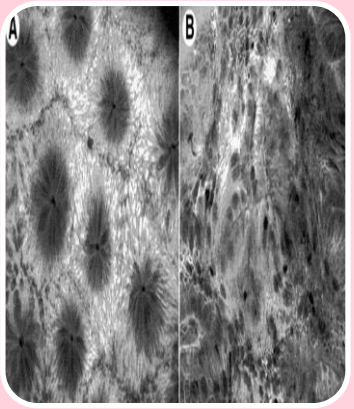
High definition (HD)

1.2 megapixel



Magnifying colonoscopy

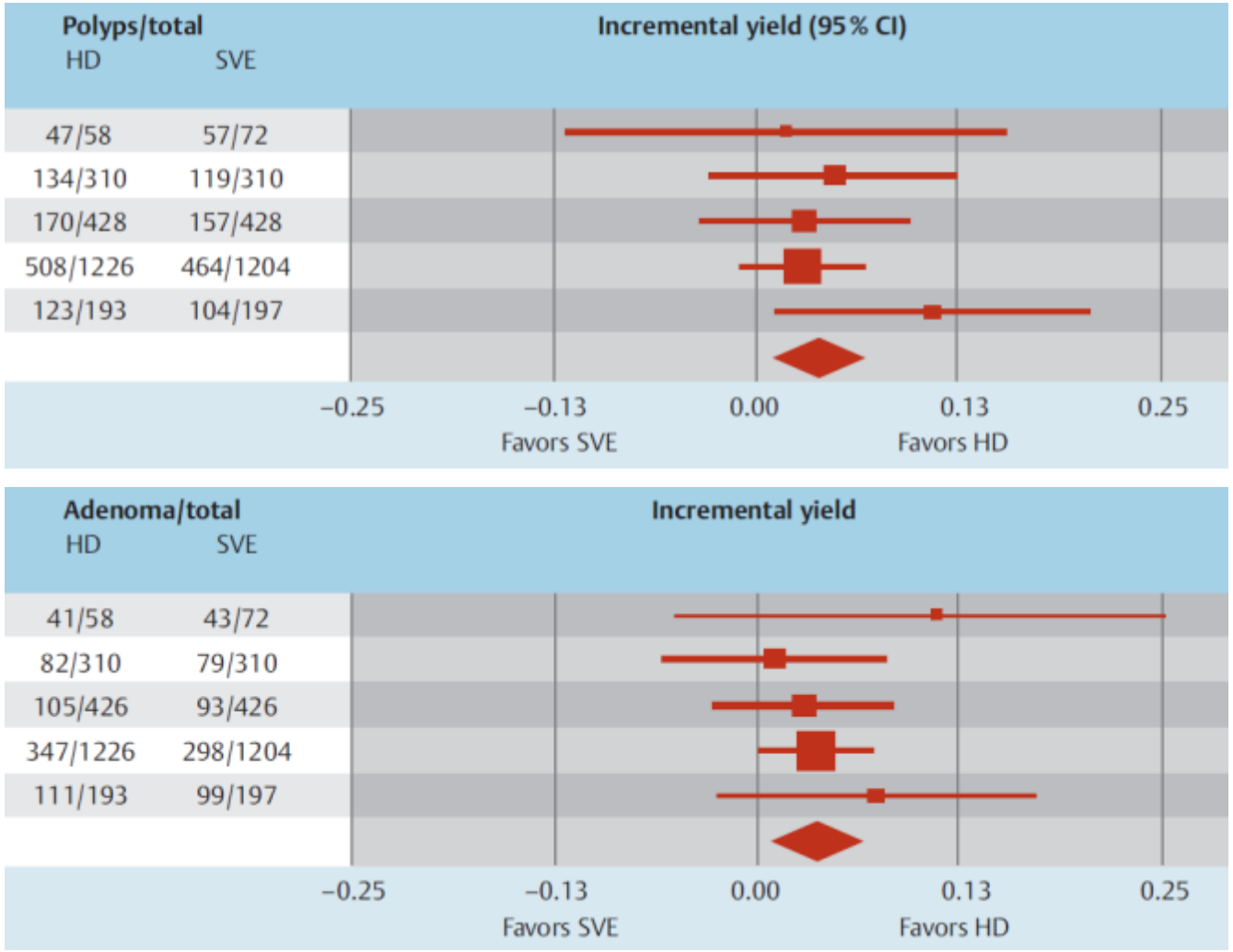
Zoom X300



Confocal Laser endo-microscopy

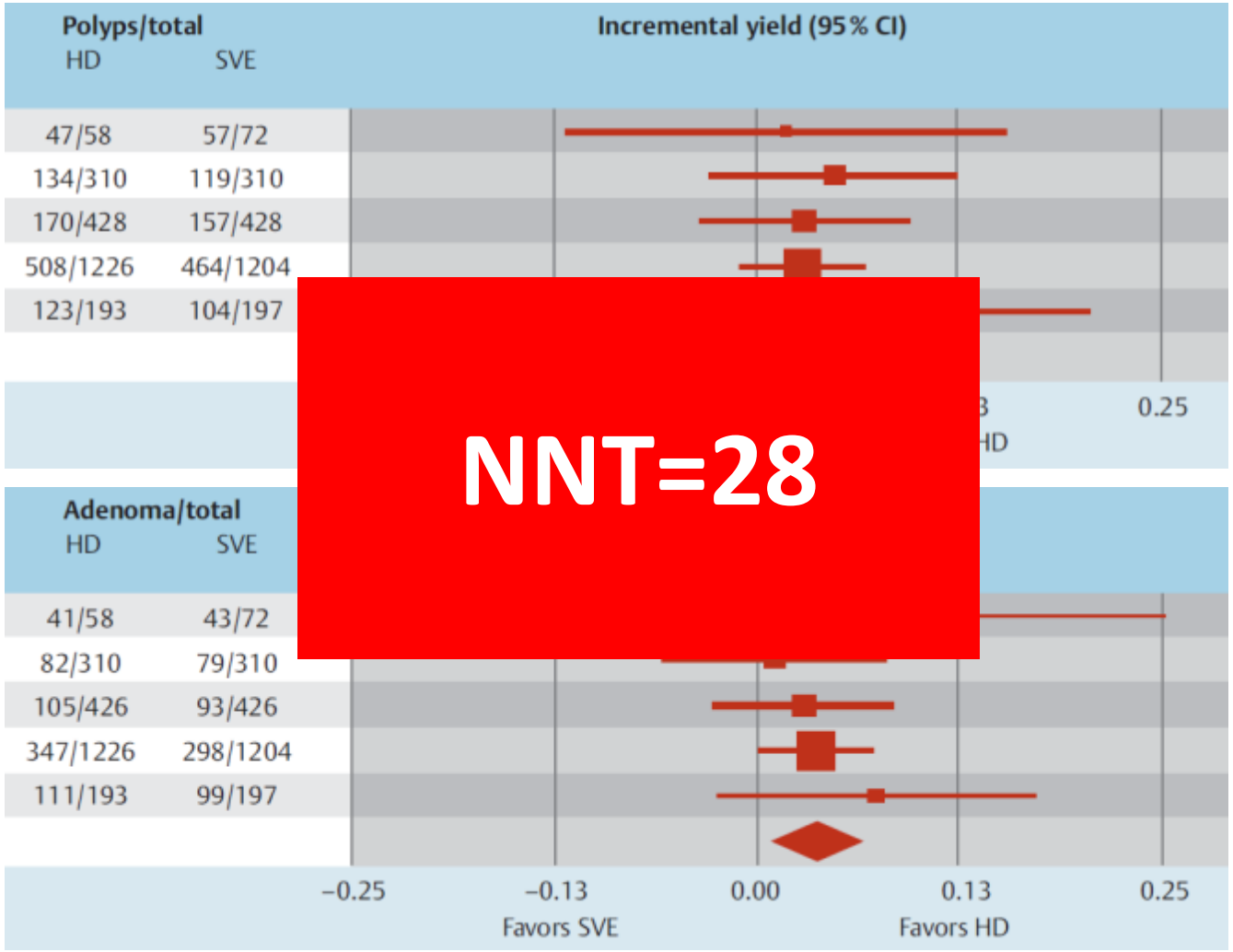
X1000

HD Colonoscopy - Meta-analysis



Subramanian et al. Endoscopy 2011

HD Colonoscopy - Meta-analysis



Subramanian et al. Endoscopy 2011

HD vs SD

Prevalence of at least one polyp in screening population: 58% (mainly hyperplastic)

Rex DK.
Maximizing detection of adenomas and cancers during colonoscopy.
Am J Gastroenterol 2006

HD vs SD

Retrospective study in routine practice.

Difference between adenomas detection HD vs SC: 28.8% vs 24.3% (p=.012)

Buchner A.
High definition colonoscopy detects colorectal polyps at a higher rate than standard white light colonoscopy.
Clin Gastroenterol Hepatol 2010

HD and wide angle vs SD

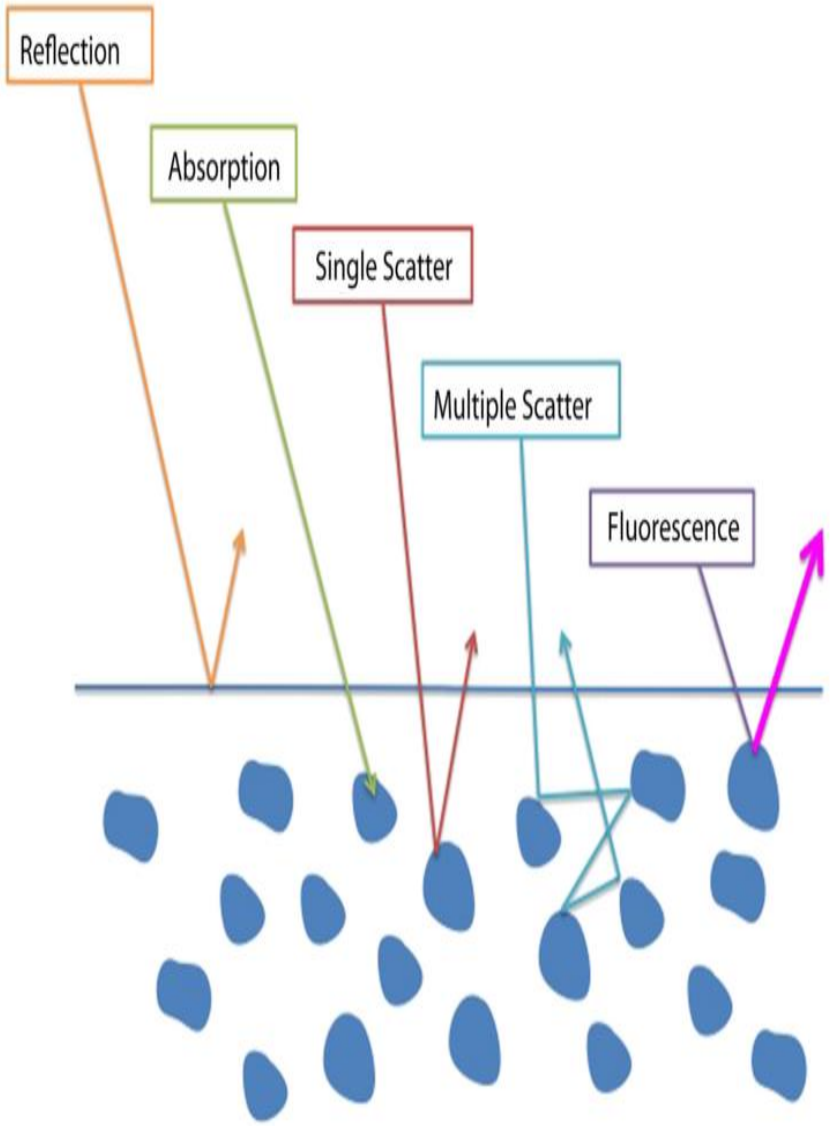
The only controlled study. No difference between adenoma detection rate

45 vs 43% (p=.87)

Pellise M.
Impact of wide-angle, high-definition endoscopy in the diagnosis of colorectal neoplasia: a randomized controlled trial.
Gastroenterology 2008

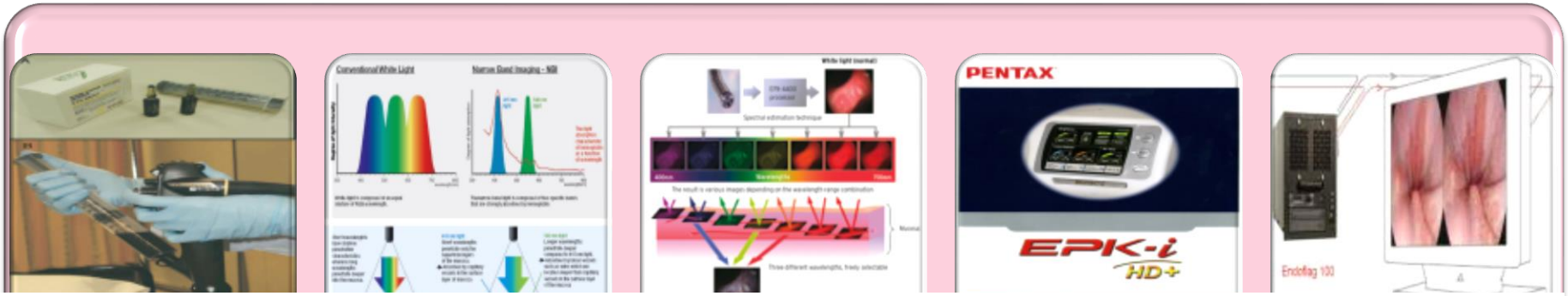
Courtesy of Prof. Halpern

Optic Imaging



- The behavior of visible ultraviolet and infrared light omitted from a source [i.e. laser, xenon] to surface is variabe
- Light may interact with tissue in various ways that can be measured and analyzed
- These interactions provide information about tissue type, Hb content, micro-structure, and molecular characteristic

Image Enhanced Endoscopy



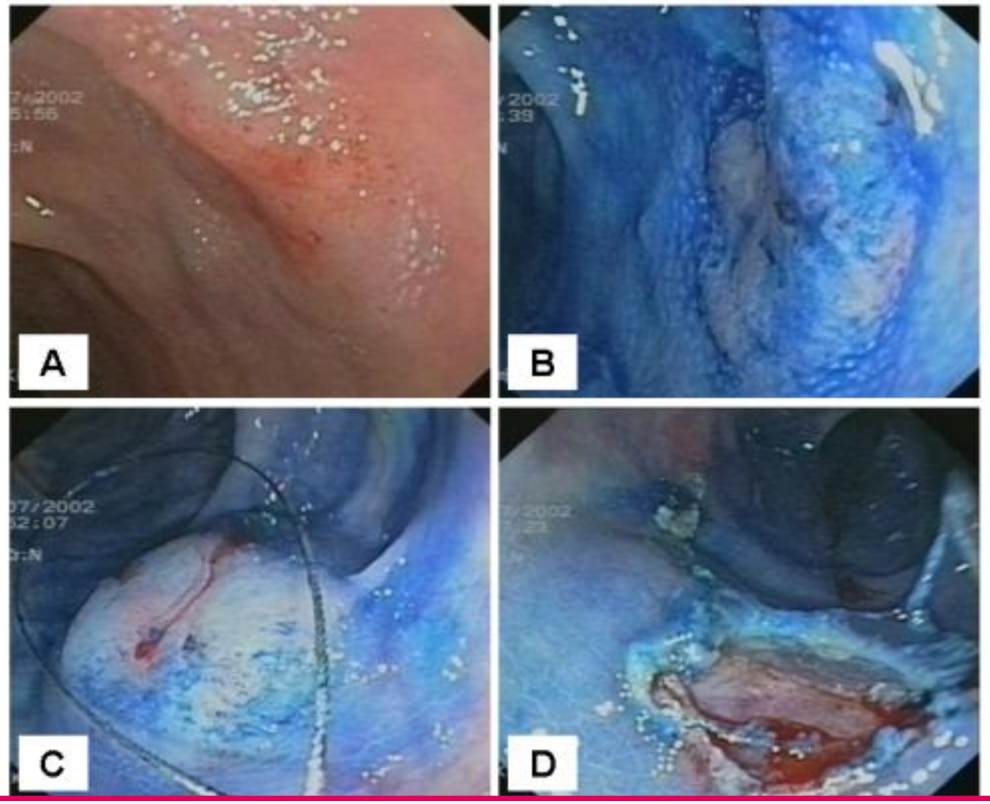
Courtesy of Prof. Halpern

Chromoendoscopy

- ***Absorptive stains***
  - **Lugol's solution**
  - **Methylene blue**
  - **Crystal violet**
  - **Acetic acid**

- ***Contrast stains***
  - **Indigocarmine**

Chromoendoscopy is Most Useful in the Evaluation of Nonpolypoid Colorectal Neoplasms (*Kiesslich, Eur J Gastroenterol 2005*)

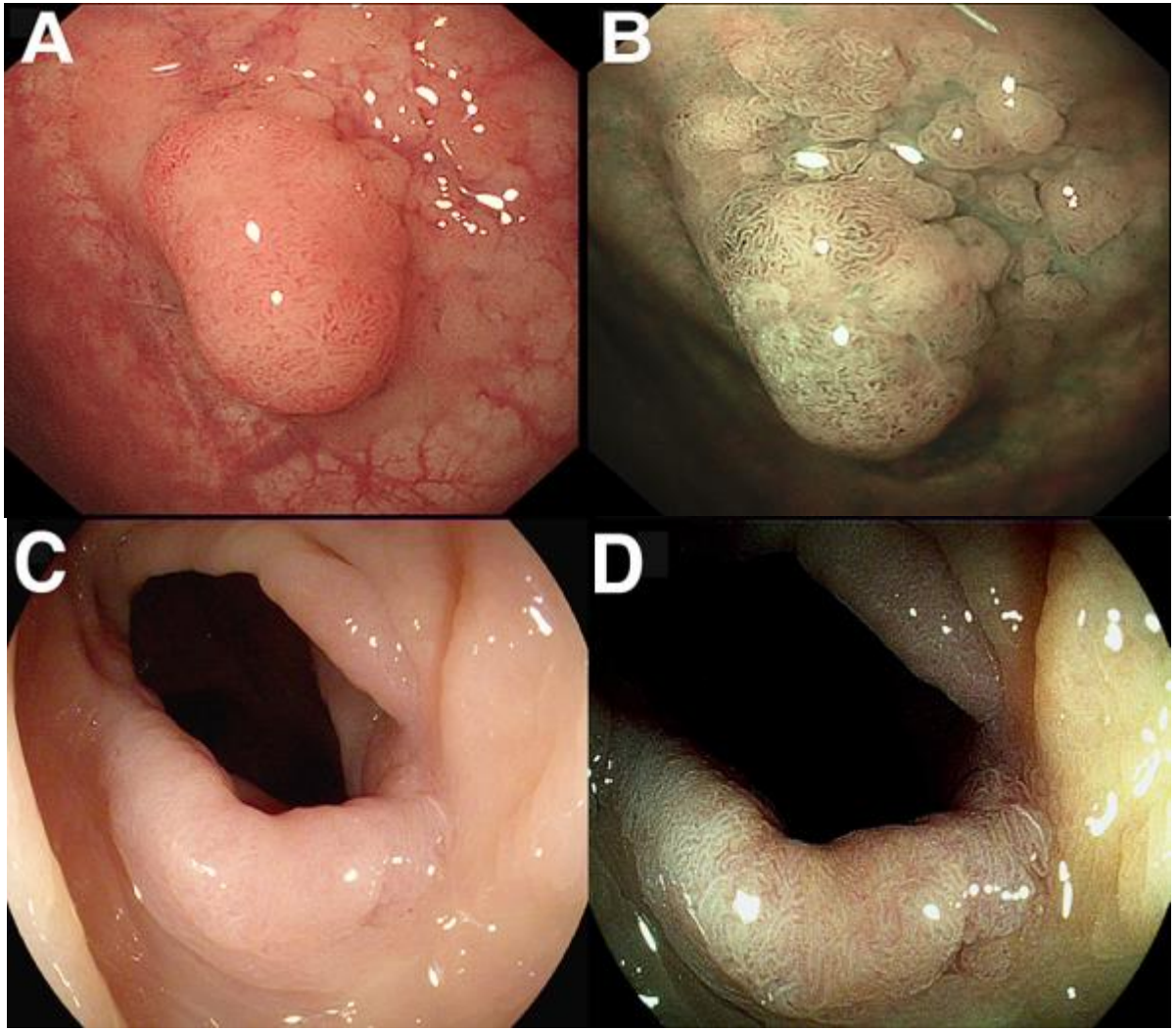


Prevalence of flat adenomas:

without Chromoendoscopy 1-5%

with Chromoendoscopy 20-35%

Electronic Chromoendoscopy?



NBI

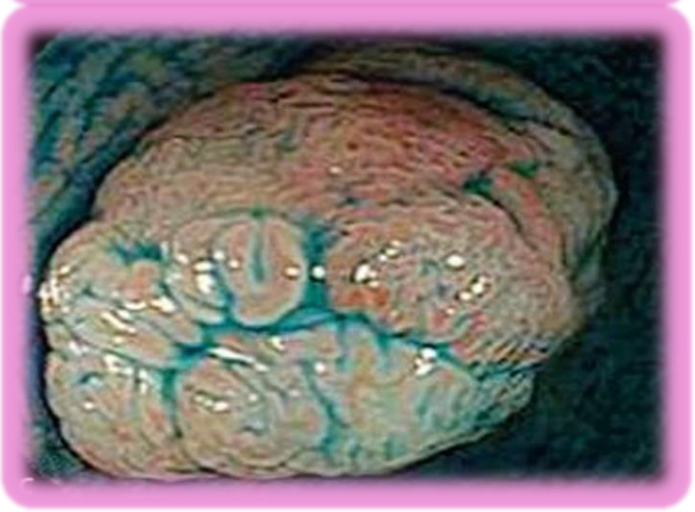
i-Scan

Subramanian et al. Clin Gastroenterol Hepatol 2013
ASGE Technology Committee. GIE 2015

Narrow Band Imaging →

CC

Chromoendoscopy →

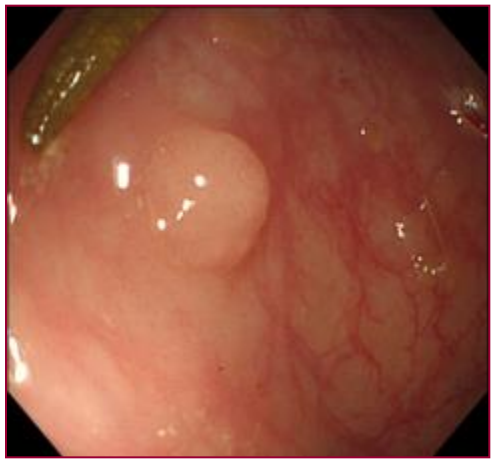


NBI is equal to chromoendoscopy for distinguishing neoplastic from non-neoplastic lesions

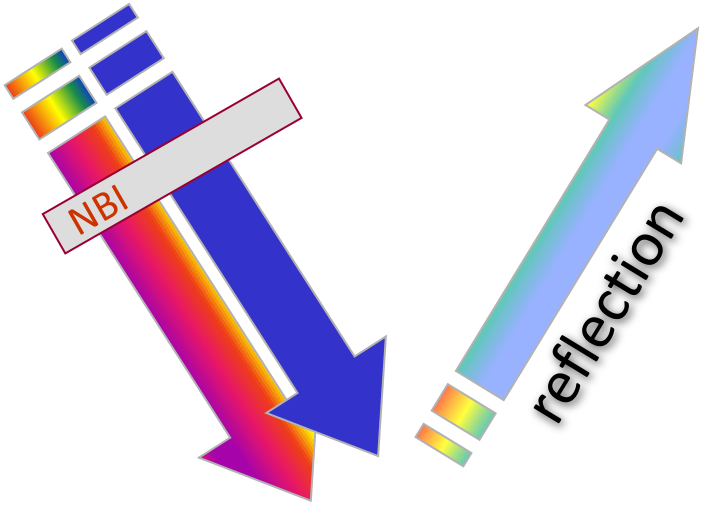
Machida, Endoscopy 2004

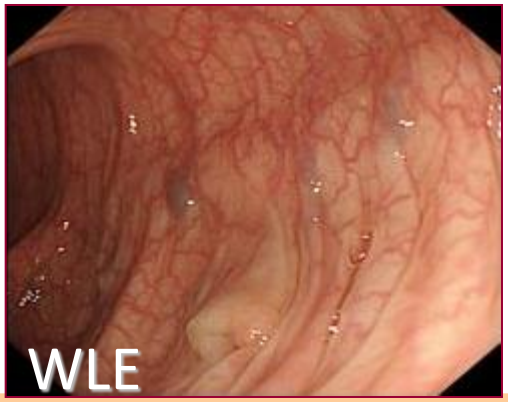
Courtesy of Prof. Halpern

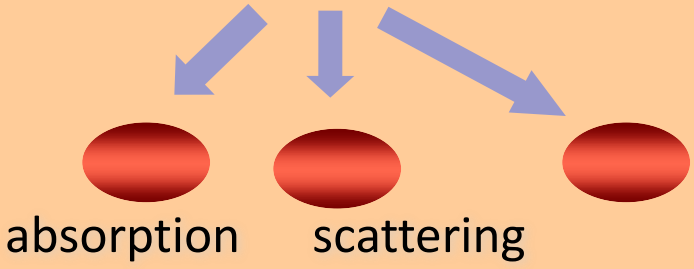
Narrow Band Imaging (NBI)



Illumination







COLON CANCER

A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia

Han-Mo Chiu, Chi-Yang Chang, Chien-Chuan Chen, Yi-Chia Lee, Ming-Shiang Wu, Jaw-Town Lin, Chia-Tung Shun, Hsiu-Po Wang

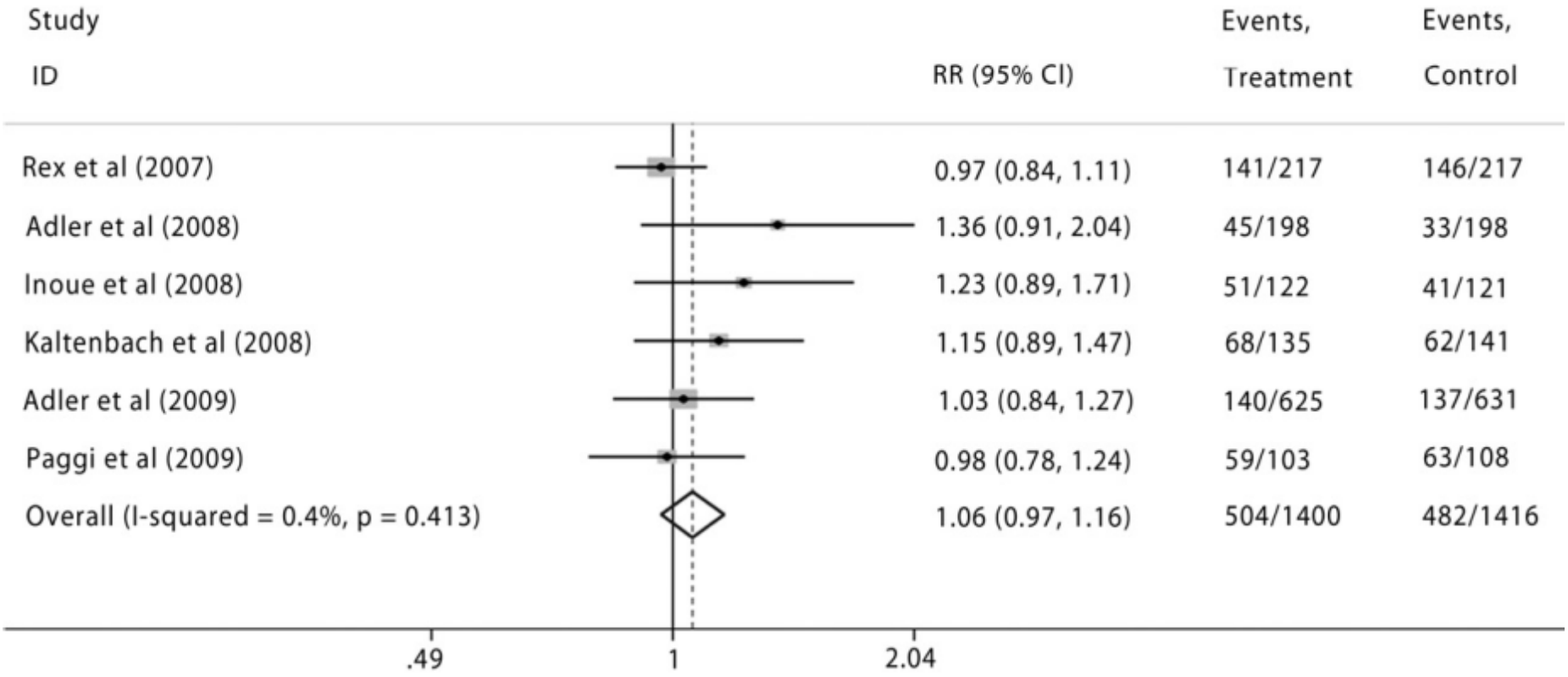
Gut 2007;56:373–379. doi: 10.1136/gut.2006.099614

Conclusions:

- *NBI can distinguish between neoplastic and non-neoplastic colorectal lesions*
- *The diagnostic accuracy of NBI is **better** than that of conventional colonoscopy and **equivalent** to that of chromoendoscopy*

Virtual Chromo (NBI) - Meta-analysis

- **Endpoint = Adenoma detection rate**



Dinesen L, et al. Gastrointest Endosc 2012

Virtual Chromo (NBI) - Meta-analysis

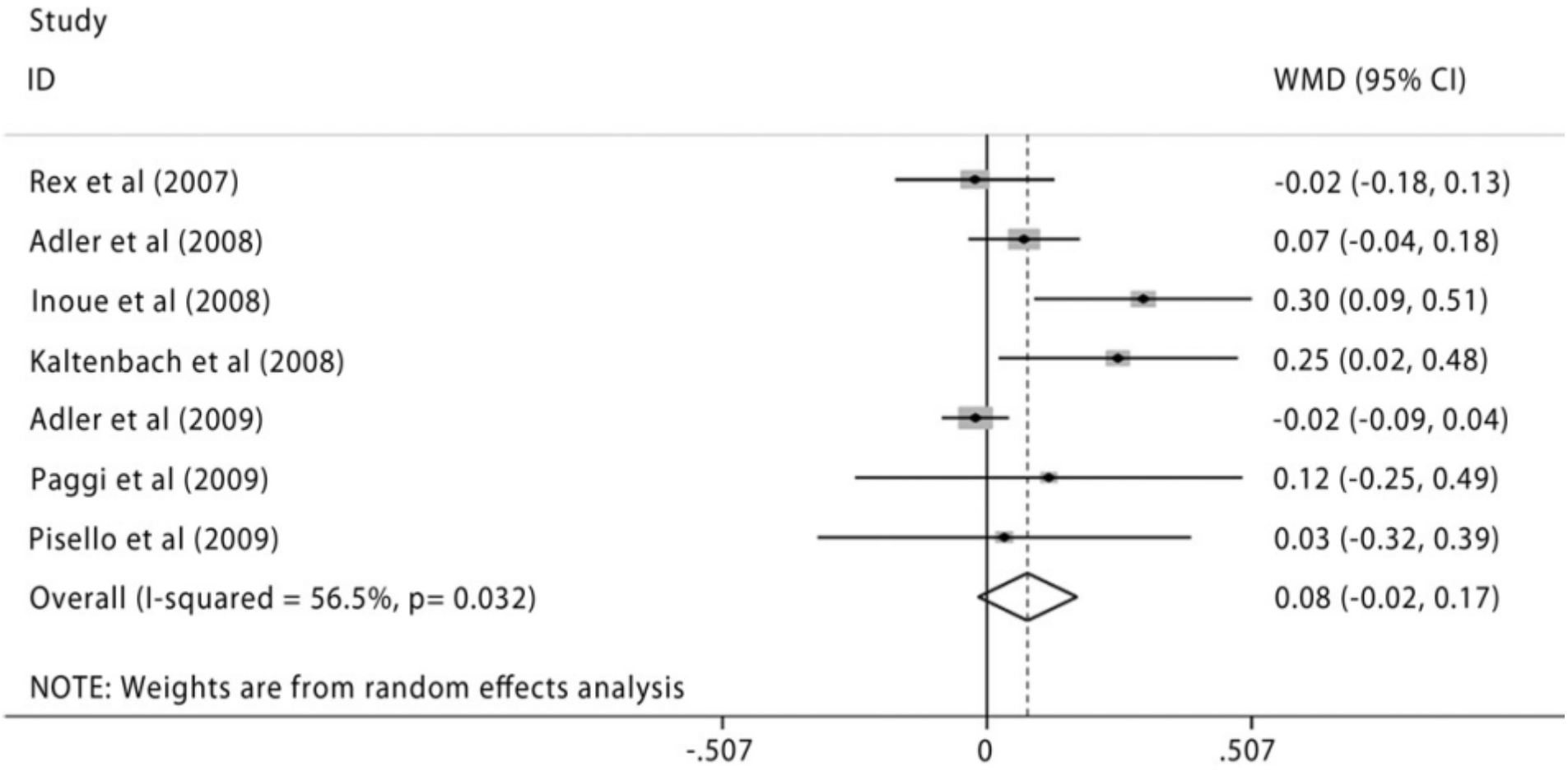
- **Endpoint = Adenoma detection rate**

No significant

Dinesen L, et al. Gastrointest Endosc 2012

Virtual Chromo (NBI) - Meta-analysis

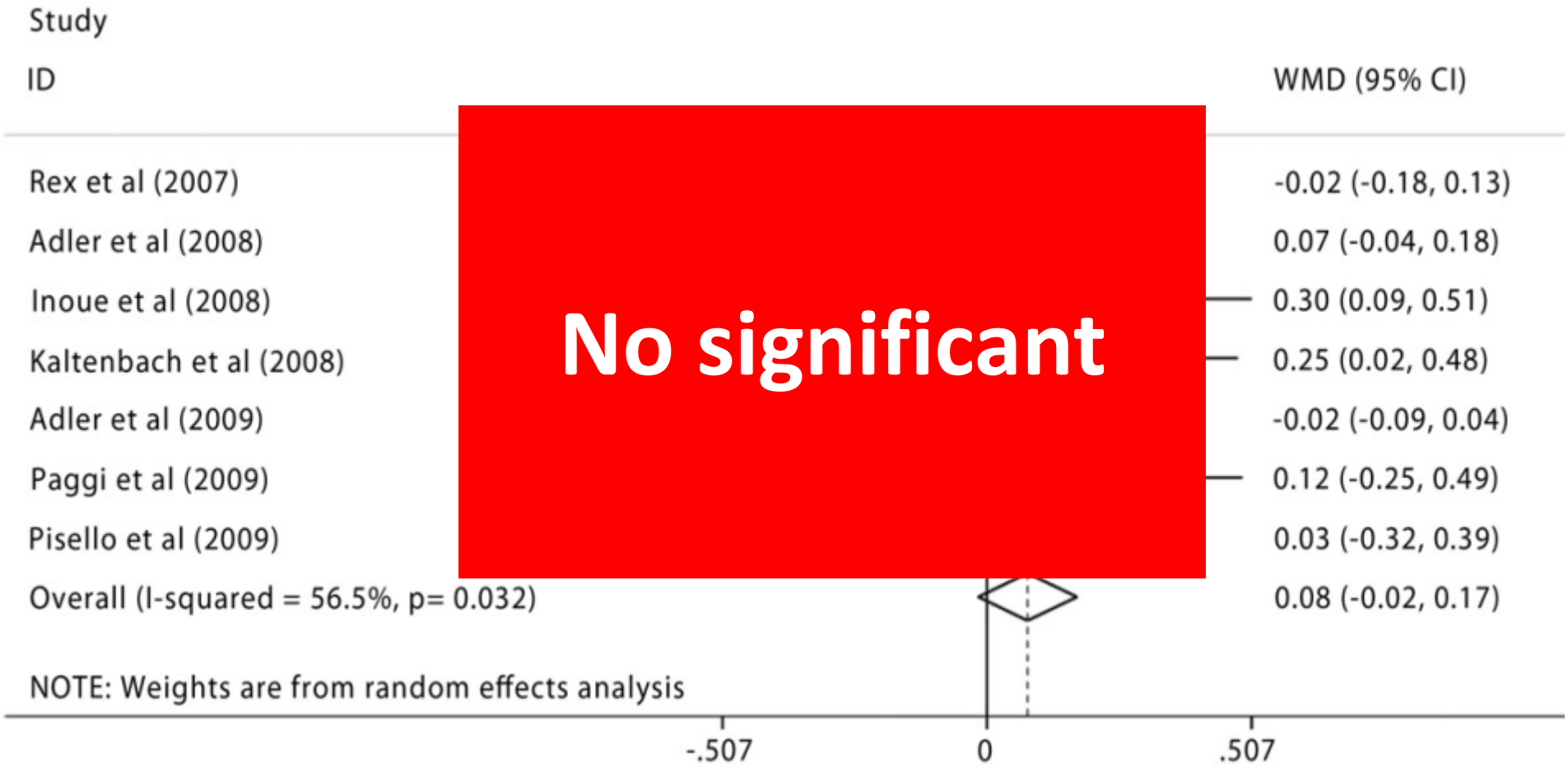
- **Endpoint = Mean adenoma per patient**



Dinesen L, et al. Gastrointest Endosc 2012

Virtual Chromo (NBI) - Meta-analysis

- **Endpoint = Mean adenoma per patient**

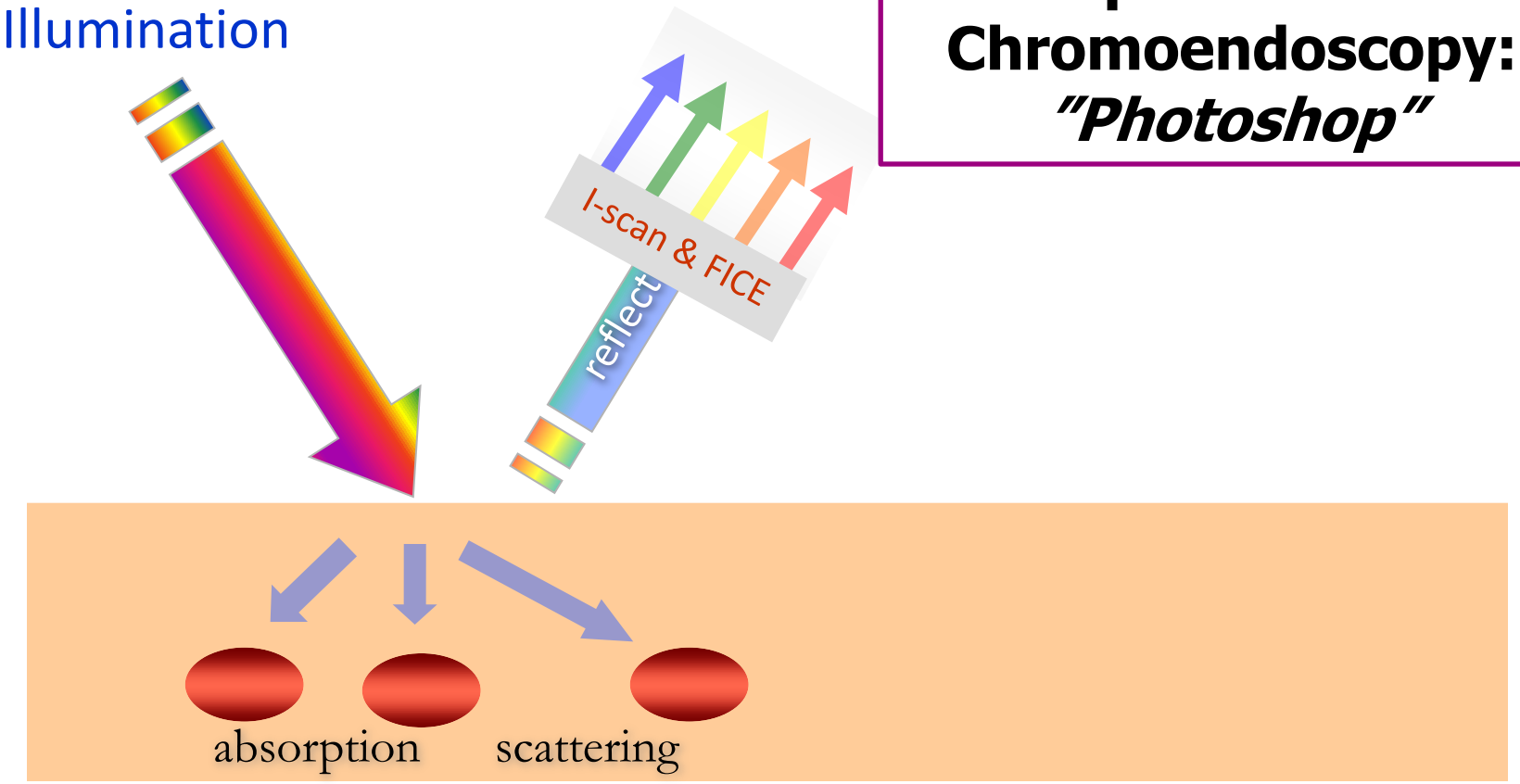


No significant

Dinesen L, et al. Gastrointest Endosc 2012

i-Scan & FICE

Computed Virtual Chromoendoscopy:
"Photoshop"

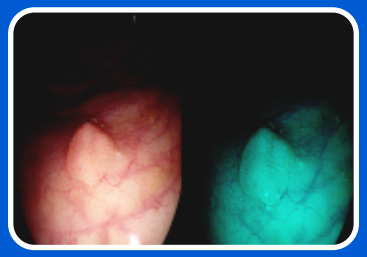


Courtesy of Prof. Halpern

iScan

Contrast enhancement (CE)

Surface enhancement (SE)



Tone enhancement (TE)

Courtesy of Prof. Halpern

Does I-scan Increase Adenoma Detection?

Hoffman, DDW 2009

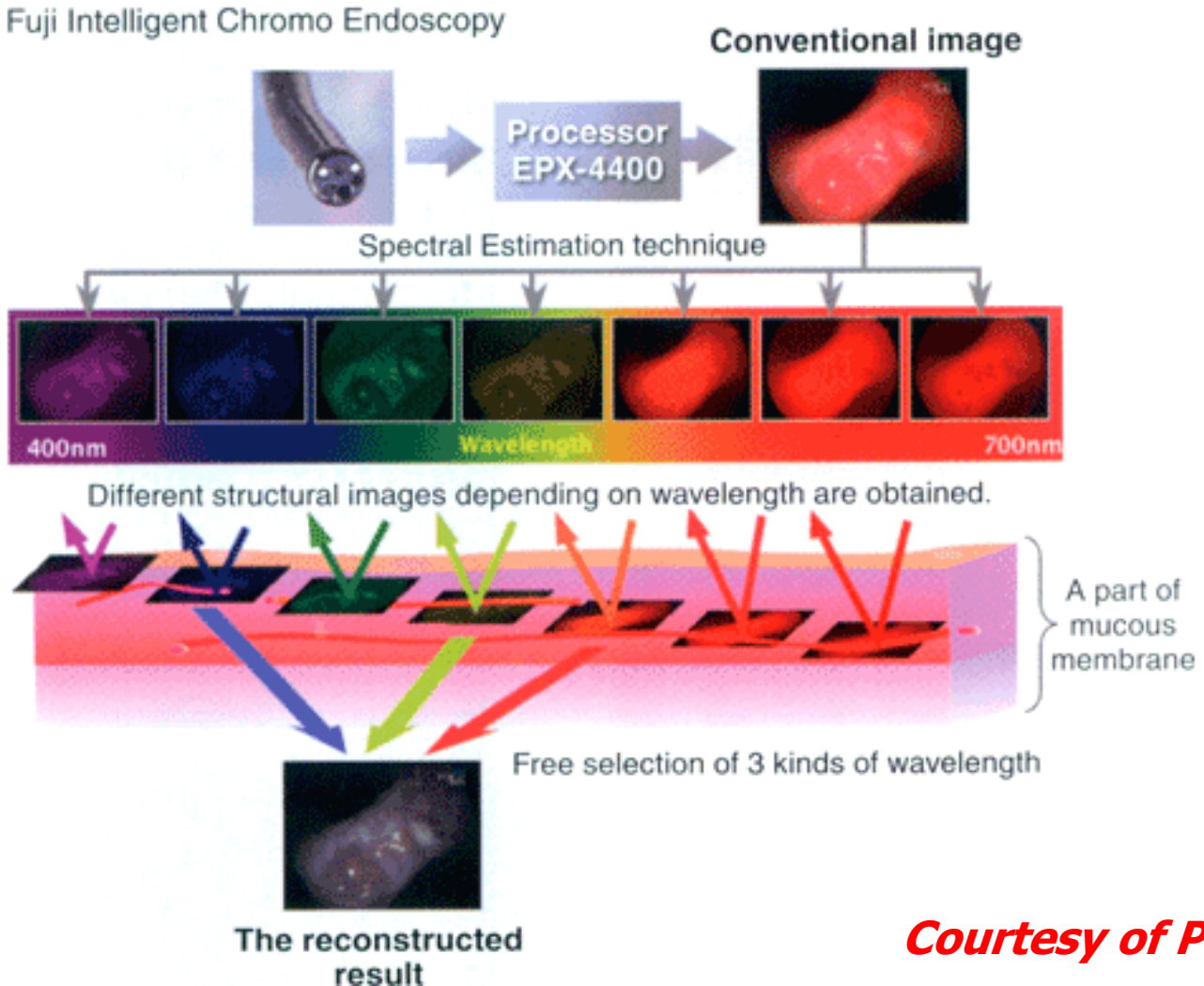
- *I-scan vs CC for detection & classification of polyps (100 vs 100 pts)*
- *Detected patients with ≥ 1 adenoma 38 vs 18 (sign. increase)*

Possibly, but not enough data

Courtesy of Prof. Halpern

Fujinon Intelligent ChromoEndoscopy (FICE)

< What is FICE >



Courtesy of Prof. Halpern

Does FICE Increase Adenoma Detection?

- ***FICE vs CC with targeted chromo 368 vs 396 pts***
- ***No difference: adenomas 236 vs 271 (p=.92)***
- ***FICE vs WLE in 63 pats***

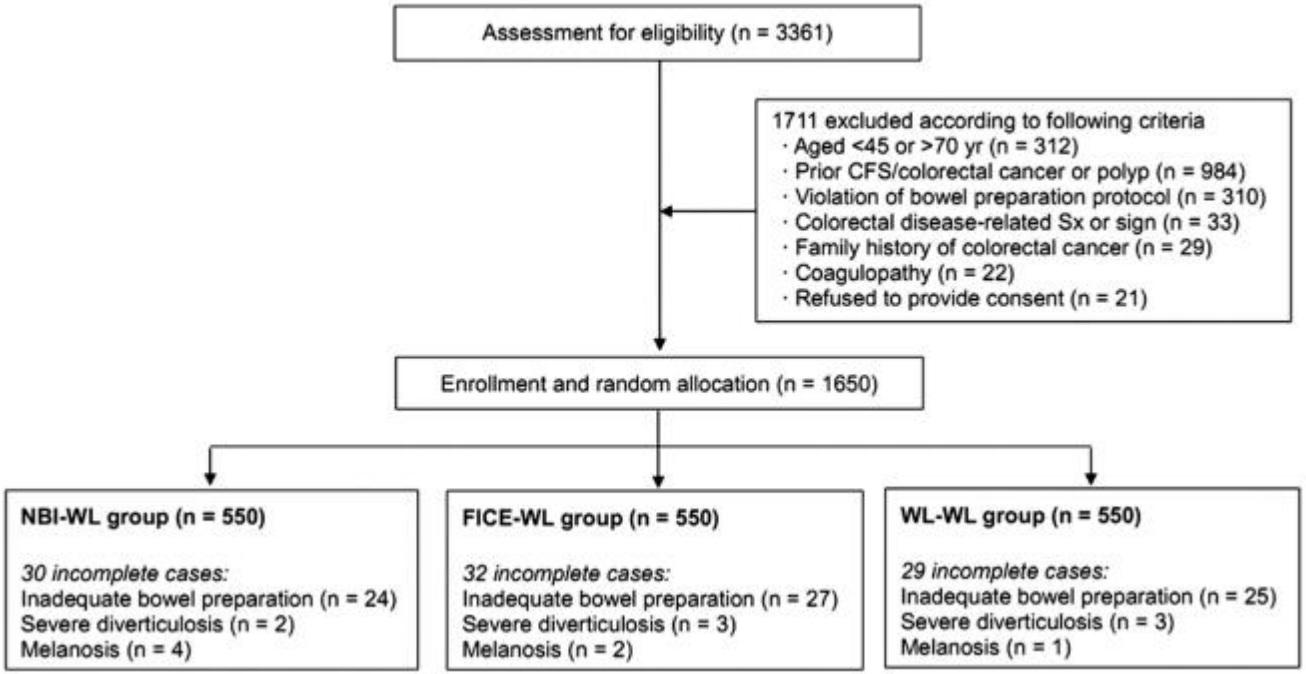
  Detected adenomas 42 vs 43 (p=.89)

Pohl, Gut 2008 Cha, Dig Dis Sci 2009

ORIGINAL ARTICLE

Comparison of detection and miss rates of narrow band imaging, flexible spectral imaging chromoendoscopy and white light at screening colonoscopy: a randomised controlled back-to-back study

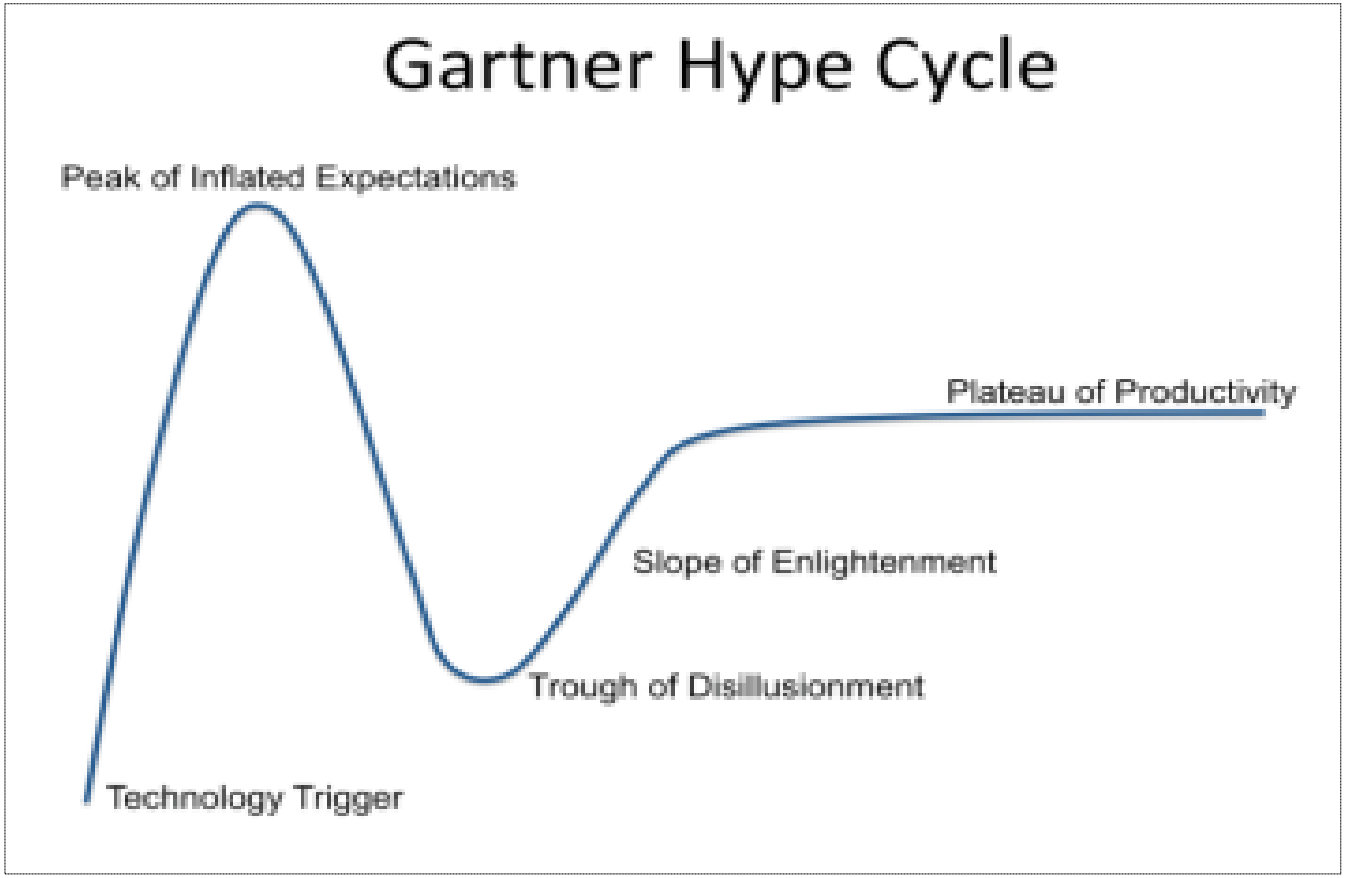
Su Jin Chung,[1] Donghee Kim,[1] Ji Hyun Song,[1] Hae Yeon Kang,[1] Goh Eun Chung,[1] Jeongmin Choi,[2] Young Sun Kim,[1] Min Jung Park,[1] Joo Sung Kim[1,2]



ADR	24%	23%	25%

Gut 2014; 63: 785-91

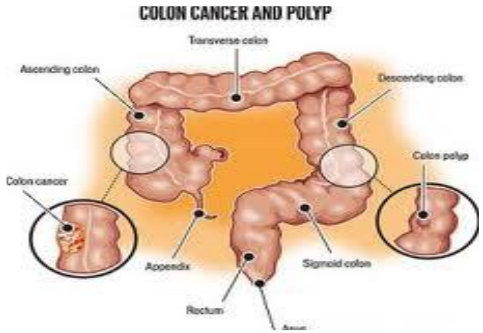
Novel Technology



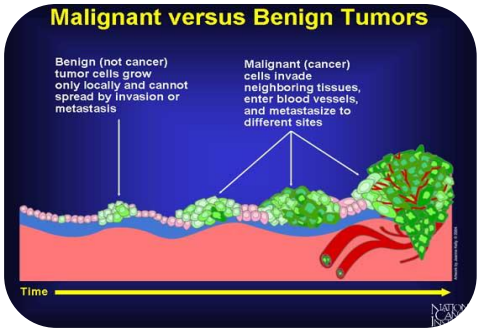
- **Study design (tandem studies)**
- **Publication bias**

Additional studies are needed!

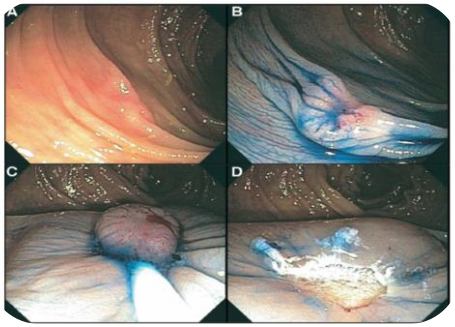
The Future is Molecular Imaging



Improved detection of tumor location

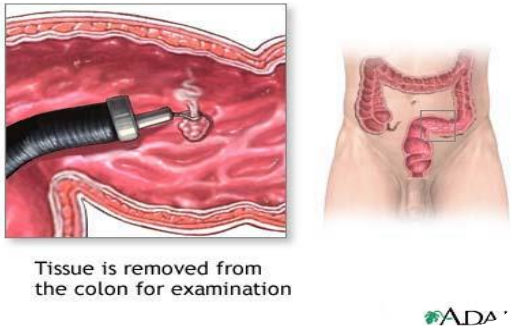


Malignant Vs Benign

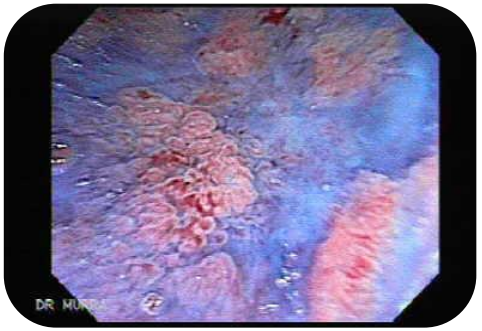


Tumor Margins

Pharmacologic al therapy [response]

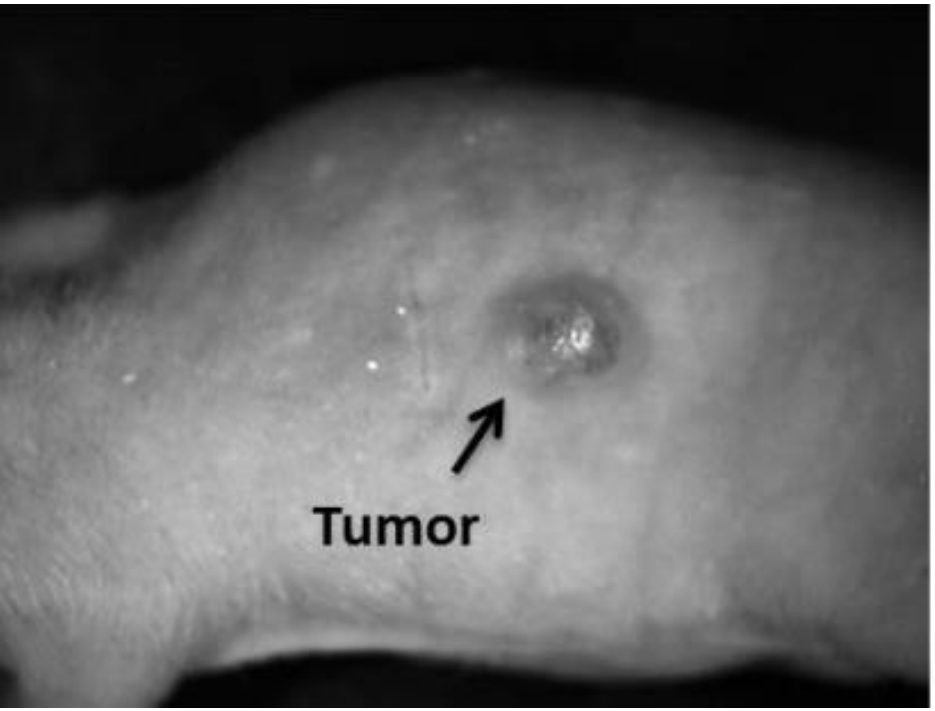


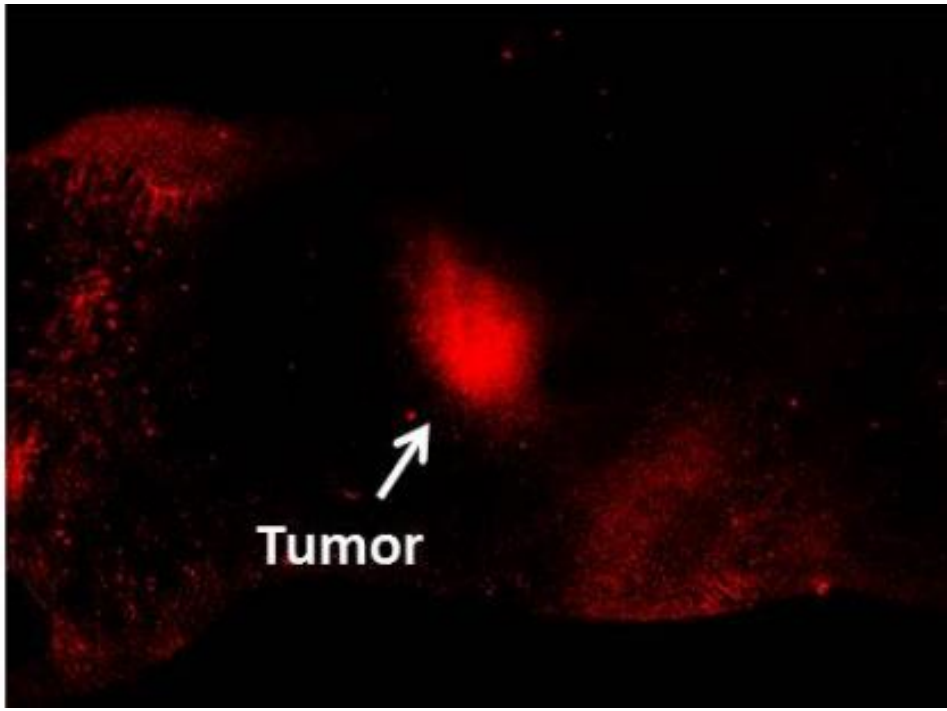
Minimize number of biopsy



Dysplasia in inflamed mucosa

mAb to CD24 concentrate in CRC in nude mice (Arber's lab)



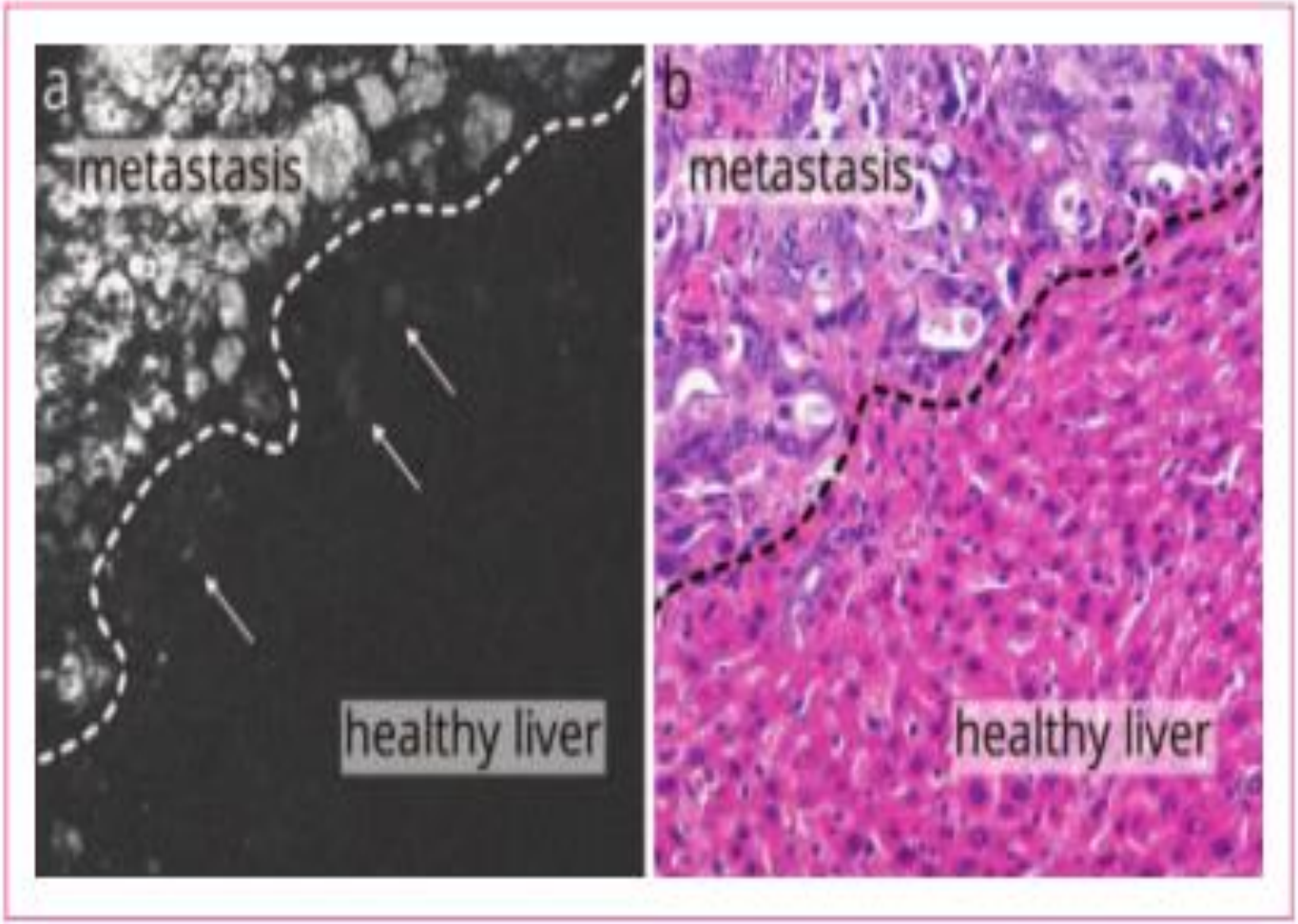


Molecular Confocal Laser Endo-microscopy Against EGFR

Molecular confocal laser endomicroscopy against EGFR using **cetuximab** identified metastases in the liver of xenografted nude mice (a).

Individual tumor cells could be visualized (arrows), surrounded by healthy liver tissue.

These findings could be verified ex vivo (b)



TECHNICAL REPORTS

nature medicine

In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease

Raja Atreya[1], Helmut Neumann[1], Clemens Neufert[1], Maximilian J Waldner[1], Ulrike Billmeier[1], Yurdagül Zopf[1], Marcus Willma[1], Christine App[2], Tino Münster[3], Hermann Kessler[4], Stefanie Maas[5], Bernd Gebhardt[5], Ralph Heimke-Brinck[6], Eva Reuter[6], Frank Dörje[6], Tilman T Rau[7], Wolfgang Uter[8], Thomas D Wang[9], Ralf Kiesslich[10], Michael Vieth[11], Ewald Hannappel[2] & Markus F Neurath[1]

Summary

1. *Colonoscopy is the gold standard*
2. *But…..we need to do even better*
3. *Exciting novel technologies are available and many more are emerging*
4. *Meticulous colonoscopy performance is crucial and still the most important parameter*
5. *Ease of use, effectiveness, economics of new technology will determine uptake in practice*